ANNALS OF SURGERY

VOL. 118 AUGUST, 1943 No. 2

TRANSACTIONS

OF THE

AMERICAN SURGICAL ASSOCIATION

MEETING HELD AT CINCINNATI, OHIO
MAY 13-14, 1943

ADDRESS OF THE PRESIDENT

THE IMPORTANCE OF FUNDAMENTALS IN SURGICAL EDUCATION*

VERNON C. DAVID, M.D.
CHICAGO, ILL.

MAY I sincerely thank you for the honor of acting as your presiding officer at this meeting. It is an office both unsolicited and unexpected but one which will ever remain a high light in the professional life of the recipient.

The subject of my address to you is influenced, as, indeed, are most of our thoughts and plans these days, by our active participation in the war. Our whole social structure is profoundly affected and is being remoulded to allow us more adequately and effectively to do our part. One aspect we feel is the impact of war on medical education and particularly on graduate education, and, with your indulgence, I shall consider some of its effects and consequences on surgical education and point out what seem to me important principles to maintain in our post-war medical educational program.

No such discussion is of the slightest value unless we win the war, and to that object the medical men of the allied countries are giving all of their energy and talents. The tradition of service has always been fundamental in the practice of medicine but is never more in evidence than in time of war. The responsibilities of family, teaching, and practice are overnight transferred to active service by those whose youth and virility permit, while the older and less active attempt to become younger and more active in all useful duties on the home front. Medical men of the United States and Canada have reason to be proud of their participation in the wars of their

* Presented before the American Surgical Association, Cincinnati, Ohio, May 13–14, 1943.

countries, and the essential necessity and quality of their services have always been recognized. We have come a long way from the beginnings of our medical service in war when, in 1775, the Provincial Congress in anticipation of war, and as one of its first acts of preparation for war, authorized the purchase of fifteen surgeons' chests, hoping to have one assigned to each regiment. At the time of the Revolutionary War there were but two medical schools in the United States (Philadelphia, 1765, New York, 1760) both of which closed during the war and, up to that time, less than fifty medical degrees had been given by them. There were, however, a number of Scotch and English doctors (among them Hugh Mercer, James Craig, and St. Clair) who had settled in America and who volunteered for service, although most of them accepted commissions in the line. To bear evidence of the quality of the medical men of those days, we are proud to remember that six doctors signed the Declaration of Independence, six became Brigadiers and several Major Generals. The First Provincial Congress of Massachusetts had twenty-two medical men as members, two of the outstanding being Joseph Warren and Benjamin Church.

The participation of medical men of the United States in the First World War is still fresh in the memories of many of us. There were 31,501 of them commissioned officers. Dr. George Brewer, in his presidential address, in 1920, recounted the services of this Association. One hundred and seven of our members held commissions in our own or allied armies. Fifty-seven served in France; 22 were decorated for meritorious service; ten received citations; and 47 served in front areas during one or more great battles.

It will, therefore, be of little surprise that about 47,000 doctors have accepted commissions in this war. From our own society fifty are commissioned officers; and many others are serving in an advisory capacity. The complete record must be left to a later and more complete summary.

The effect of war on medical education is the tendency to lower standards in the preliminary education of medical students, to accelerate their medical instruction, and to greatly reduce graduate education. All of these factors hold the threat of lowering the quality of medical education which, in turn, limits the effectiveness of the medical man both in war and peace. While perhaps in a degree necessary because of war, the threatened curtailment of premedical education strikes at the very foundations of education for, in order for the physician of the present or future to take his proper place in our social structure, he must not only write plainly and read understandingly but he must have some knowledge of what has happened to the world in the past in order to help build soundly for the future. Doctors today play an important rôle in prescribing for society and its institutions as they relate to public health as well as to care for bodily ills.

The accelerated medical curriculum leaves no time for the student to interest himself in other than routine work, and the short period of internship and greatly curtailed resident system obviate to a large degree training

and investigation carried out in the scientific laboratories. Our middle-aged group of surgeons who have attained their graduate training have been promptly and properly inducted into the Army and Navy, with a consequent disorganization of many of our hospitals, teaching, and dispensary staffs that leaves the older ones of us in the saddle doing our best to carry on with the determination to maintain our medical instruction at the highest level possible, and to prosecute investigation in problems arising in war medicine. The most serious results to medical education lie in the curtailment of a sufficient period of graduate training and especially as it relates to continuation of training in the fundamental science branches as applied to surgical problems.

If the war lasts several years, there will go out into military service 10,000 to 20,000 young medical men who have had no other graduate training than one year of internship. Canada's effort to recall from military service some of the most promising young medical men to teaching hospitals for a year of resident training, as a reward for meritorious service, is a worthy one and is now being considered by our Navy. This would not only serve as a reward for outstanding service but would render a picked group further education which would be of signal service to the Army and Navy but would insure to post-war medicine a needed lift in quality.

On the assets side of the war ledger are many human values as well as some educational ones. In addition to the pride of service during war, our young medical men in war will soon develop a sense of organization under trying conditions, will become more self-reliant, will develop the power of quick decision, and will place a high value on the simple fundamentals of life as loyalty, self-sacrifice, and team work, which go far to develop a sound viewpoint which from now on will be of necessity a world viewpoint. Never before have circumstances and inclination combined more effectively to solidify our North American ideals, policies, and scientific objectives.

With the war won, and our medical men returned to peace time activities, we will be faced with many difficult problems for solution of which I shall only consider the continuation of graduate training. The mental unrest following sustained war effort, the change of pace and objective in the day's work, the necessity of reestablishment of home and sustenance, the changed emphasis on the values of life will make for temporary disorganization in the lives of our returning medical men, but we should not forget it is to that group that we must look for the medical leadership in the post-war days. The outstanding men in surgery during the past twenty years were practically all men who had risen to their responsibilities in war service in the First World War. We must see to it that for a similar group returning from this war important posts are made available in our medical schools and hospitals and that they are made to feel our confidence in their ability to reestablish and maintain high medical educational standards. A very large group of men having had one year of internship will go to war without resident training. Some of these men will continue active professional work in Army or Navy

assignments but many will return to civil life with more worldly but little medical experience. It is to be hoped that from this group many can be chosen for resident training or be given assignments in the fundamental science laboratories so that their war age-group may be given the educational advantages which provide the creative and imaginative mind with the necessary tools for advancement of our knowledge in medicine.

The selection of such a group for further training will test our most mature judgment, for the factors of their experience and ability in war surgery must be weighed in the balance with available facilities and the proper number of carefully trained specialists deemed essential in our medico-social structure. Above all, training of specialists requires, more than ever before, thorough grounding in the basic sciences.

It may not be without interest to briefly trace the importance of fundamental science training in the development of surgery as a specialty. While surgery has been practiced from the earliest times, as we know from the description of trephining and splinting in the 17th Century B.C. Smith Papyrus (which itself was a copy of an ancient Egyptian manuscript), the main incentive to the development of surgery was the care of war casualties. Hospitals appeared from 1100 to 1700, and there was an increasing tendency to train surgeons in them. The history of St. Bart's Hospital, London, founded in 1123, gives an impressive procession of such events. A certain amount of surgical specialism developed in bloodletting, treatment of fistula by John Ardene (1306–90), and cutting for stone by Cheselden (1688–1752). It was as late as 1731, however, that the Royal Academy of Surgery of Paris was founded, which was entirely devoted to surgery and, in 1745, that the surgeons of England split entirely from the Barbers' Guild.

Scientific surgery was brought to London by William and John Hunter. Before their time surgery was an art dealing with individuals, as the late Sir Darcy Powers so aptly said. William Hunter gave his first course of anatomy in 1746, and founded the Great Windmill Street School of Anatomists. Numbering among its pupils were Hewson, Sheldon, Cruikshank, and Ballie, and resulting from its work were definite advances in our knowledge of the circulatory and lymphatic systems. Its teachings produced surgeons of the caliber of Abernathy, Astley Cooper, and John Hunter, of London, Hey, of Leeds, and our own Philip Syng Physick, of Philadelphia. John Hunter and his pupils took a wide view of surgery, and in their studies explored the architecture of the bodies of animals as well as man, and founded a school of surgery that was devoted to investigation and advancement of knowledge mainly through anatomic and pathologic channels, for at that time chemistry was in its infancy and physics was first beginning as a science, and the compound microscope was not in use.

In the Royal College of Surgeons in Edinburgh is now housed the collection of anatomic dissections of Sir Charles Bell. His interest and investigations in the anatomy of the nervous system, carried on for fifteen years in the Great Windmill Street School, resulted in the description of both

the external respiratory nerve and peripheral seventh nerve palsy in 1821. Later his "Anatomy of the Brain" gave an entirely new concept to the physiology of nervous tissue.

In France and Germany continuing wars were a hindrance to the development of scientific surgery but developed great technical surgeons, as Dupuytren, Larrey, and Bardeleben. Working as an assistant to Dupuytren was a young man who observed with interest and curiosity that the application of Dupuytren's spur-crushing clamp applied to the open end of opposing loops of bowel did not cut through the bowel to cause peritonitis. He pondered on what caused the opening surfaces of the bowel to agglutinate. As a result of many experiments on animals, Lembert described, in 1826, the agglutination of opposing peritoneal surfaces by fibrin, and devised the Lembert suture, which principle has made gastro-intestinal surgery possible.

Largely as a result of the inspiration and training acquired in these first beginnings of scientific surgery in London, Edinburgh and France, Morgan, Shippen and Rush founded the first medical school in this country in Philadelphia in 1765. The Warrens became the leaders of surgery in Massachusetts, founded Harvard Medical School in 1783 and the Massachusetts General Hospital in 1811, which later, in 1846, in Warrens' Clinic, became the setting for the first public demonstration of ether anesthesia. McDowell returned from Edinburgh to Kentucky to perform the first ovariotomy in 1809.

Samuel D. Gross, a founder and first president of this Association, published, in 1828, a translation of Boyle and Hollard's "Manual of General Anatomy" followed, in 1830, by a book of his own, "The Anatomy and Physiology and Diseases of Bones and Joints," which he said was "to discharge in part that debt which, according to Lord Bacon, every man owes to his profession."

The development of the science of physics gave great impetus to the development of eye surgery when, in about 1831, von Helmholz invented the ophthalmoscope. A young group of well trained general surgeons, by their scientific attainments, placed ophthalmic surgery on a high level. Argyl Robinson, who became the great eye surgeon of his time, was first a house surgeon and later taught physiology.

Surgical pathology made great progress after the development of the compound microscope, from 1812 to 1830, and schools of thought developed around Virchow and, later, Cohnheim in Germany, Billroth, in Vienna, and Sir James Paget, in England. Students were attracted from many parts of the world and they, in turn, spread the gospel of sound pathological training as fundamental to good practice of medicine.

As late as 1864 the causes of fermentation, putrefaction, and suppuration in wounds was unknown, and in that year Pasteur exploded the theory of spontaneous generation as a cause of putrefaction. This fundamental work almost immediately attracted the attention of Joseph Lister, whose early education may be of some interest in emphasizing the importance of training in the basic sciences in preparing the creative clinician.

Joseph Lister (born in 1827) had an illustrious father, a merchant by occupation, but with many scientific interests. He was especially concerned with the development of the acromatic lens of the microscope. In his medical education Lister early came under the guidance of Sharpey in physiology and, later, Nolan in chemistry, both of whom had a great influence in his understanding of wound healing. He then had a sound course of clinical instruction under James Syme, Professor of Surgery at Edinburgh. His earliest papers in Edinburgh were on duration of vitality in tissue, early stages of inflammation, gangrene, coagulation of the blood, the function and structure of nerves regulating contraction of arteries—all basic studies which reflected the breadth of his thought and training. In Glasgow he had a large service in traumatic surgery and became intimately acquainted with the consequences of infection and the enormous mortality following wounds or surgical operations. A most natural reaction was his interest in, and study of, the distressing sequelae of wound infection, gangrene, and death. Therefore, following Pasteur's announcement and during the incumbency of the Edinburgh chair (1869–77) he was largely concerned in working out the principles and details of the antiseptic methods which revolutionized surgical procedures. Pasteur's work found Lister in an advantageous position to appreciate the importance of his work as it related to wound infection. Lister's contributions were no accident but were made possible by his training in basic science, and found him with the tools in his hands to apply Pasteur's great discovery to the prevention and treatment of wound infection.

Due largely to the extraordinary work of Pasteur and Lister and augmented materially by further contributions in bacteriology, pathology, physiology, and chemistry by Koch, Virchow, Johannes Mueller, Claude Benard and Liebig, antiseptic and then aseptic surgery became firmly established in the last half of the 19th Century. During the lifetime of most of us there has developed with startling rapidity the extension of surgery to every part of the body, bringing new problems for solution, both fundamental and technical, which has resulted in the greatest wave of specialism surgery has ever seen. In addition to the older specialties, neurosurgery, thoracic surgery, plastic surgery, vascular surgery, and reconstruction surgery have made progress that has been phenomenal. As one would expect, the most important contributions have come from men who have had the broadest training in general surgery, surgical principles, and in the basic sciences. All of us have been witnesses and many of you have been participants in the advance in our knowledge of shock, hemorrhage, coagulation of the blood; maintenance of fluid balance, blood electrolites and plasma protein; wound healing; transplantation of tissues; treatment of infections, decompression of the gastro-intestinal tract; surgical bacteriology; pathology and growth phenomena of tumors of the bone, gastro-intestinal tract, lung, and ductless glands. We have also witnessed visualization of the gastro-intestinal, biliary and urogenital tracts, blood vessels, lung, and brain, but to mention some of the most important contributions.

The wide diversities of interest or specialism in surgery is but a natural outcome of its increased horizon and to maintain a proper prospective in its proceedings, the American Surgical Association has in recent years elected to its membership leaders in the various fields of special surgery. This policy should be continued for it affords this Association an opportunity to assume leadership in influencing further and proper development of specialized surgery. The danger of inbreeding specialism rears its head where specialists train specialists to the point of attrition of sound general principles. This can be avoided by insisting that specialism should be synonymous with maturity based on training in the fundamentals both scientific and technical, which so often leads to advance in knowledge.

The establishment of American Boards for certification of specialists surely had these principles in mind. In General Medicine, the requirement of broad training in general medicine before certification of specialists in cardiology, gastro-enterology, allergy, *etc.*, must be preceded by certification by the Board of General Medicine. In surgery, however, the only special group required to have prior certification in general surgery are the proctologists. This does not and should not infer that the surgical specialty boards are not in complete accord as to the value of training in the basic sciences and principles of surgery. It does indicate, however, that we have gone our respective ways without having established a common denominator in requirements of basic training which is essential to all surgery. Could we not with profit to the future value of our surgical certifying boards meet together with an object of unifying our standards for surgical training and to take a firm position against the establishment of additional specialty boards until we have well integrated our present problems. As a first step in indicating our mutual belief in the value of training in the basic sciences, would it not be well to consider giving a single examination for all the surgical specialty boards covering principles of surgery as wound healing, hemorrhage, coagulation of the blood, thrombosis, anesthesia, surgical infections, fluid balance, as well as concepts of anatomy, physiology, chemistry, bacteriology, and pathology as applied to surgery in general. This examination would be but a preliminary requisite to the other examinations required and given by the several surgical specialty boards but would at once tend to unify our requirements in the fundamentals. I am sure we are all interested, first of all, in developing sound surgeons whose subsequent interest in special fields will be tempered with breadth of vision so essential to sound progress and the establishment of new frontiers. As an encouraging beginning, the American Boards of Orthopedic Surgery and General Surgery are now discussing the desirability of having a single preliminary examination in fundamentals which candidates must pass before taking the further examinations required by each of the two Boards.

As an added impetus to keeping our medical instruction as well as our specialties firmly based on the fundamental sciences, I have felt for a long time that our medical curriculum should be reorganized to still further merge

the preclinical and clinical years. Theory and practice could well be closer integrated. As we now plan to give our most promising residents and associates additional training in the fundamental sciences so that they may have at their command the science methods so necessary in the study of basic aspects of disease, why should not the fundamental science departments in turn send one or more of their well trained young men into the wards of our teaching hospitals? There they would find already established for study living pathology of tumor growth, ulceration of the gastrointestinal tract, stone formation, circulatory disease, problems relating to ductless glands, anesthesia, and all varieties of infections, to mention but a few of the problems awaiting solution. The stimulating and regulating effect of the study of disease by clinician and fundamental scientists working side by side is well known to medical lore. One has but to peruse that delightfully written "Short History of Cardiology," by James B. Herrick, to appreciate the rôle that anatomy, pathology, physics and clinical bedside knowledge has played in intimate teamwork in advancing our knowledge and recognition of diseases of the heart and circulatory system. After describing the mutual stimulation afforded to Rokitansky, the pathologist, and Skoda, the clinician, in their work, he quotes Rokitansky's remarks on relinquishing the chair of pathology to the effect that his work in pathologic anatomy was only the foundation for scientific investigation in the sphere of medicine and a basis for a science of pathologic physiology.

The classic study of the physiologic aspects of arteriovenous aneurysm, by Sir Thomas Lewis, was carried out on patients. The outstanding physiologic contributions of Ivy, Mann and Best on the stomach, liver and blood coagulation, have enlisted the enthusiastic cooperation of the clinical departments and have pointed the way to further fact-finding studies in which scientific laboratory methods can be applied to the living patient.

It has never seemed to me entirely sound to have our science departments so often divorced from our teaching wards. In clinical teaching we have long since abandoned the dry quiz class exercises dealing with theory and more and more have introduced our students to patients in the wards in whose study and care they have taken an increasing part. In addition to the clinical investigation carried on by our own staff men in our hospitals and laboratories, would it not be helpful and stimulating to student, staff and science worker alike to have the latter also carrying on investigative work in our hospital wards in the field of his choice? As Helmholtz, the eminent physiologist and physicist said: "The purpose of science is to comprehend reality, for the investigator wishes to know what his work has done for the great problems of human life." It would be hard to deny that it would be profitable to bring the fundamental study of anatomy closer to clinical medicine. It is my impression that there are relatively few teaching hospitals where the bacteriologic study of surgical infections and so-called routine bacteriologic examinations reach a high level of exactitude. It is not possible in every clinical department to have clinicians fundamentally trained and

with sufficient free time to adequately cover the possibilities for study of disease from the anatomic, physiologic, bacteriologic, chemical and pathologic standpoints, and it seems logical to me to develop more of an overlap of interest in problems of the sick patient between clinical and science departments. I venture to suggest that this closer integration between theory and practice in medicine would be easier to attain if the heads of our science departments were doctors of medicine as well as holders of degrees in their respective science departments.

In the post-war days, when funds for graduate training will undoubtedly be less, it would also be economically sound to promote an overlap in the interests and activities of clinical and fundamental science departments which would in no way interfere with their basic functions but which would promote an even exchange of personnel who are interested in investigation. The value of such contacts to the student clerk in the ward would surely broaden his viewpoint and emphasize the importance of scientific companionship in care of the patient and study of his problems.

It is significant that other professions are experimenting with the idea of bringing their students studying theory into contact with practice. For some years the University of Cincinnati has sent their student engineers from a period of work in college out into industry for a few months and has then brought them back to the laboratory. Northwestern University has recently dedicated a large engineering school to that system of instruction. Mr. Kettering, of the General Motors research staff, speaking on that occasion, emphasized the importance of this principle due to the variations occurring in the application of theory to practice as well as to the understanding of the human elements involved. Basic advances in medicine in the past have been the result not only of creative but well trained minds. It is probably beyond human understanding to develop the former but it is possible to afford opportunities for sound training in the fundamental sciences as well as in technical fields.

It is my thesis that in the difficult post-war days, a large share of our funds and efforts should be expended in giving such opportunities to as many worthy candidates as possible; that our surgical specialties should mutually maintain a broad base in fundamental science requirements in an effort to keep their viewpoint a wide one. It is my hope that we may seriously discuss the feasibility and desirability of bringing theory and practice closer together in our medical curriculum.

The long, hard grind to obtain a sound training may discourage some but the stout heart which condones no short cuts will recognize the advantage of quality in training. The young man planning for his graduate training in surgery should be helped to realize how important it is that he should come into active participation in clinical surgery not only with a knowledge of his subject from the diagnostic and technical side but should bring as a part of his tools for work a special knowledge of one or more of the fundamental sciences of medicine which at once will give him a useful

background for the study of some basic aspect of disease. Equally applicable to prosecution of the war for the maintenance of freedom and our way of life as well as to our efforts to maintain and improve educational standards are the words from "Pilgrim's Progress."

> "Some have thought there may be a passage forthwith to their father's house with no more hills and valleys to go over, but the way is the way and let this suffice."

In conclusion, I wish it were given to me to adequately express this Association's pride in and admiration for the young men and women of our country who, at home and in distant lands, are carrying on the finest traditions of service. A while back we were inclined to worry about our younger generation and their reactions to our unsettled society. Today we have occasion to bless them not only for their deeds but for the realization that our country and its institutions are safe indeed in their hands. Sharing fully in their valor and high service are our colleagues in medicine now in the armed forces. Today we especally salute our fellow members of the American Surgical Association who are giving all of their energy and talents to the problems centering around prevention of disease and the rehabilitation of our sick and wounded. They are writing another worthy chapter in the annals of this Association.

THE STUDY OF THE PREVENTION OF INFECTION IN CONTAMINATED ACCIDENTAL WOUNDS, COMPOUND FRACTURES AND BURNS*

FRANK L. MELENEY, M.D.†
NEW YORK, N. Y.

TWO YEARS AGO, at a meeting of the American Surgical Association, a paper was read by title which outlined a plan for the study of war wounds. The plan called for ten units in as many different cities, each unit to be fully equipped with clinical and laboratory facilities to care for and study cases of civilian accidental wounds, compound fractures and burns which would simulate war casualties. All of the wounds were to be treated basically by as complete a surgical débridement as possible. The débrided tissue was to be sent to the laboratory for a complete analysis of the bacterial flora. A limited number of different kinds of local and general treatment, with a proper series of controls, were to be employed to appraise, if possible, the newer chemotherapeutic agents in the prophylaxis and in the treatment of wound infection. Careful observations and records were to be made of the course of wound healing and particularly of any evidence of infection. If infection developed, its nature and etiology was to be determined by further laboratory studies and the cause of the failure of the preventive measures was to be analyzed. A carefully prepared summary sheet was planned to contain all of the available data from the record of the case which might indicate what factors favor or minimize the development of infection. These data could then be transferred to punch cards for statistical analysis.

Six months later the plan was finally approved by the Committee on Medical Research of the Office of Scientific Research and Development but it was limited to eight of the original ten units. Before the personnel could be mobilized and equipment purchased, Pearl Harbor was bombed and we were at war. The question of the best way to use the new chemotherapeutic agents in war wounds still remained unanswered because it had been impossible to evaluate the drugs in England. The rapid evacuation of patients from hospital to hospital in a centrifugal manner had made it difficult to follow cases from the beginning to the end of the treatment.

On February 1, 1942, the eight units began to function. The original plan was altered to a considerable extent by the reports which came back from Pearl Harbor. Observers who saw the casualties there were profoundly impressed by the low incidence of wound infection, which they believed to be due to the copious application of sulfanilamide to the wounds.

* Read before The American Surgical Association, Cincinnati, Ohio, May 13–14, 1943.

† Representing the Subcommittee on Surgical Infections of the National Research Council, and the responsible investigators of the Contaminated Wound and Burn Project. under the Committee on Medical Research of the Office of Scientific Research and Development, Doctors Guy Caldwell, Warfield Firor, Charles Johnston, Sumner Koch, John Lockwood, Perrin Long, Champ Lyons, Roy McClure, Alton Ochsner, Mont Reid, and Frank Meleney, Chairman.

Our original plan called for observation on control cases without drugs and other controls receiving treatment with local bacteriostatic agents other than the sulfonamides. But, said the Pearl Harbor observers: "You cannot withhold from these patients the benefit of the sulfonamide drugs."

Instead of twelve different categories to cover the whole field as we originally planned, we reduced the range of our investigation to one principle method of treatment, with one optional control. In so doing, it was recognized that we might have all of our eggs in one basket and find, after a period of time, that the basket would fall and the eggs be broken.

During the period of our delay, sulfadiazine had come into use. It was found to be less toxic than sulfanilamide, less nauseating than sulfapyridine, and less likely to block the kidneys than sulfathiazole. Its range of antibacterial activity was thought to be as wide as any of the other drugs and it was, therefore, decided upon as the drug of choice for systemic administration. For local application it was decided to use equal parts of sulfanilamide and sulfadiazine powder on the theory that the sulfanilamide in a concentration of 1000 mg.% would be active for several days before it was absorbed. The more slowly absorbable sulfadiazine would then continue to act over a long period of time, possibly as long as ten or fourteen days.

Seven of the eight units undertook to study all three of the major categories of injuries, namely, soft-part injuries, compound fractures and burns, while the eighth concentrated on burns.

With regard to burns there were strong advocates for three different methods of treatment. These were (1) the tannic acid method; (2) the vaseline compression dressing method; and (3) the sulfadiazine in triethanolamine spray. A fourth experimental method was permitted each of the units.

No attempt was made to dictate procedures. The surgeons were directed to perform as complete a débridement of the wounds as possible, but beyond that they were given full liberty to decide other details of the treatment. In those units in which non-drug treated controls were used, every care was taken that there should be no selection of control or treated cases but that they should alternate regularly.

Great care was taken to make accurate observations and careful records so that we would know just how the cases were handled. It was decided that all those having the care of the patient should determine, as a group, whether or not infection had developed and whether it was trivial or serious. The criteria of infection included not only the bacteriologic findings but the clinical evidence of inflammation, namely, redness, swelling, pain, fever, undue exudate, necrosis of tissue, or delay of wound healing. There may have been differences of opinion on individual cases but we believe that, on the whole, the personal equations have been pretty well neutralized. As the responsible investigators of the different units have gathered in Washington to talk over their experiences, it has been obvious that all of the units have had similar experiences and remarkably similar results.

The summary sheets were completed as soon as possible after the healing of the wound had taken place. Preliminary reports were sent in on all com-

pound fractures within two months and changes have been incorporated later in the record if infection or delayed bone healing supervened.

As the records came in, the data were transferred to punch cards and were then analyzed according to common factors. For the most part, it was possible to divide the case into two or three groups within each category, for example, they were separated into those having maximum and those having minimum gross contamination and similarly maximum and minimum tissue damage. Those operated upon within three hours were compared with those operated upon after three hours. With regard to wound closure, three groups were compared, namely, wounds left open, wounds partially closed and wounds completely closed. And so forth with all of the factors which we thought might play a rôle in favoring or minimizing the incidence of infection. In each of these groups the number and percentage of trivial and serious infections have been determined. As the summary sheets steadily accumulated in the central office the number of cases in each group steadily mounted and it became necessary to apply the statistical formula which biostatisticians use to determine whether percentage differences are statistically significant or may be due merely to chance.

The records from the first 1500 cases have been summarized in the present report. These include 682 wounds of the soft parts, 471 compound fractures, and 347 burns. Each group has been dealt with separately, although they have much in common when it comes to a consideration of those factors which tend to favor or minimize the incidence of infection. These factors inherent in wounds and burns have been well known to surgeons for a long time, and they have known many ways of aiding nature to ward off infection. A study of this kind would not be warranted at this time if some new method of combatting infections had not come to light which must be thoroughly evaluated with respect to war wounds and burns.

With the advent of the newer chemotherapeutic agents, the surgeon now has the opportunity of applying to the wound surfaces or administering internally a bacteriostatic agent. However, these may not be used without some risk of toxicity to the blood forming organs, liver and kidneys. Furthermore, it is known that certain conditions may be present in wounds and burns which may inhibit the bacteriostatic action of these drugs.

The results are shown in the accompanying table.

TABLE I

INCIDENCE OF INFECTION IN 1500 CASES DIVIDED INTO THE THREE MAIN CATEGORIES

	Totals	% Infected	
Soft-Part Wounds			
Totals	682		
Serious infection	38	5.6	
Trivial infection	74	10.9	16.5
Compound Fractures			
Totals	471		
Serious infection	55	11.7	
Trivial infection	47	10.0	21.7
Burns			
Totals	347		
Serious infection	66	19.0	
Trivial infection	80	23.1	42.1

SOFT-PART WOUNDS

We find an incidence of 16.5 per cent of infection in soft-part wounds as a whole with twice as many trivial as serious infections. There is no clear-cut division between these two groups, for one shades off into the other.

TABLE II

PERCENTAGE OF INFECTION IN COMPARABLE GROUPINGS IN 682 SOFT-PART WOUNDS

	Totals	% Infected	
		Serious	Trivial
Shock	166#	10.8*	13.8
No shock	509#	3.9*	10.0
Maximum tissue damage	340#	8.0*	13.2
Minimum tissue damage	341#	3.2*	8.5
Maximum gross contamination	245	7.8*	13.9
Minimum gross contamination	437	4.4*	9.2
Operation before three hours	413#	3.4*	10.7
Operation after three hours	266#	9.0*	11.3
Maximum washing	178#	8.4*	18.0
Minimum washing	502#	4.6*	8.4
Complete débridement	431#	4.6*	9.2
Incomplete débridement	216#	7.4*	14.4
Wound left open	57	1.8*	10.5
Partial closure	58	12.1*	19.0
Complete closure	567	5.3*	10.1
Partial or complete closure with tension	55#	14.7*	16.4
Partial or complete closure without tension	375#	5.3*	8.8
Tendon repair	114#	9.6*	10.5
No tendon repair	403#	2.7*	11.2

Data incomplete.
* Statistically significant.

Serious infections are associated significantly with shock, with heavy gross contamination and with severe tissue damage. Operation after three hours, incomplete débridement and prolonged washing are associated with a high incidence of infection. The figures for prolonged washing are surprising. These results may indicate that washing of a dirty wound before débridement may disseminate the organisms throughout the wound, and irrigation all during the operation may wash organisms in from the surrounding skin and further damage tissue. Wounds which are partly closed showed a higher figure than either those left open or those completely closed. This may mean that partial closure frequently had sutures under tension or the surgeon had grave doubts that the wound should be closed. In this series the completely closed wound cases were ten times as numerous as those left open or those partially closed. Closure under tension, when that was noted, frequently seemed to play a major rôle in the occurrence of infection. Tendon repair cases show a high rate of infection and the sulfonamide drugs have not lowered this rate. By every method of grouping these cases from the point of view of chemotherapy, we can find no evidence that either sulfanilamide or equal parts of sulfanilamide and sulfadiazine locally or sulfadiazine generally with or without the local use of drugs have cut down the incidence of local infection. It is true, however, that the incidence of septicemia or of death is extremely low in this series and it may be fairly stated that the spread of infection from the local site has been minimized, for

TABLE III

INCIDENCE OF INFECTION IN DRUG TREATED CASES AND IN COMPARABLE CONTROLS IN 682 SOFT-PART WOUNDS

	Totals	% Infected	
Local Sulfanilamide and Sulfadiazine in equal parts	188		
Serious infection	8	4.3	
Trivial infection	23	12.2	16.5
Local Sulfanilamide	197		
Serious infection	13	6.6	
Trivial infection	31	15.7	22.3
Total local Sulfonamide	397		
Serious infection	23	5.8	
Trivial infection	54	13.6	19.4
No local drug	281		
Serious infection	14	5.0	
Trivial infection	20	7.1	12.1
General Sulfadiazine	452		
Serious infection	27	6.0	
Trivial infection	56	12.4	18.4
No general Sulfadiazine	223		
Serious infection	10	4.9	
Trivial infection	17	7.6	12.5
General Sulfadiazine without local Sulfonamide	81		
Serious infection	6	7.4	
Trivial infection	4	4.9	12.3

cases which have become infected either during the administration of drug or without preliminary drug treatment have all been given systemic sulfonamide treatment, if, and when, they could tolerate it.

TABLE IV

SOFT-PART WOUNDS

Total 682 — Death from Infection, 2—Both Wounds Closed

	Case I	Case II
Lesion	Avulsion of scalp.	Stab wound of chest, abdomen, diaphragm, stomach.
Operation	Débridement, closure with tension.	Débridement, closure without tension.
Primary drug	0	Sulfanilamide locally. Sulfadiazine generally.
Secondary drug	Sulfadiazine	Sulfadiazine
Cause of death	Meningitis	Empyema
Day of death	24th +	3rd
Principle organisms	Coag.-pos. staph., *B. pyocyaneus*	Hemolytic strept., Group F.

There were only two deaths from infection, or 0.3 per cent. One developed meningitis on the 24th day after an avulsion of the scalp. No primary drugs were used. The other died on the third day following a stab wound of chest, diaphragm and stomach from a Group F. hemolytic streptococcus emphyema. Primary drug was used, both locally and generally.

TABLE V

SHOWING THE NUMBER OF CASES YIELDING HEMOLYTIC STREPTOCOCCI IN THE DÉBRIDED TISSUE, THE NUMBER IN WHICH THIS ORGANISM PERSISTED AND THE NUMBER OF CASES IN WHICH THIS ORGANISM APPEARED AS A NEW CULTURE, WITH AND WITHOUT SULFONAMIDE TREATMENT

Soft-Part Wounds—682

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser.	Triv.		Ser.	Triv.		Ser.	Triv.
Hemolytic Strep.	36	16.7	25.0	5	40.0	60.0	12	41.6	25.0
Gen'l. sulf.	29	20.7	27.6	5	40.0	60.0	11	36.4	27.3
No. gen'l. sulf.	7	0	14.0	0	0	0	1	100.0	0
Local sulf.	26	15.4	30.8	4	25.0	75.0	11	36.4	27.3
No local sulf.	10	20.0	10.0	1	100.0	0	1	100.0	0

TABLE VI

SHOWING THE NUMBER OF CASES YIELDING COAGULASE-POSITIVE *Staphylococcus aureus* IN THE DÉBRIDED TISSUE, THE NUMBER IN WHICH THIS ORGANISM PERSISTED AND THE NUMBER OF CASES IN WHICH THIS ORGANISM APPEARED AS A NEW CULTURE, WITH AND WITHOUT SULFONAMIDE TREATMENT

Soft-Part Wounds—682

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser.	Triv.		Ser.	Triv.		Ser.	Triv.
Coag.-Pos. *Staph. Aureus*....	58	8.6	19.0	15	20.0	60.0	44	20.4	59.1
Gen'l sulf.....	46	8.7	21.8	14	14.3	64.3	36	22.2	61.2
No gen'l. sulf.....	12	8.3	8.3	1	100.0	0	8	22.5	50.0
Local sulf.....	45	6.7	22.2	14	14.3	64.3	34	14.7	64.7
No local sulf.....	13	15.4	7.7	1	100.0	0	10	40.0	40.0

TABLE VII

SHOWING THE NUMBER OF CASES YIELDING PATHOGENIC GRAM-NEGATIVE AEROBIC BACILLI IN THE DÉBRIDED TISSUE, THE NUMBER IN WHICH THESE ORGANISMS PERSISTED AND THE NUMBER OF CASES IN WHICH THESE ORGANISMS APPEARED AS NEW CULTURES, WITH AND WITHOUT SULFONAMIDE TREATMENT

Soft-Part Wounds—682

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser.	Triv.		Ser.	Triv.		Ser.	Triv.
Pathogenic Gram-neg.									
Aerobic Bacilli.....	162	8.6	12.3	27	33.3	37.0	19	36.8	52.6
Gen'l. sulf.....	114	9.6	14.0	21	33.3	42.9	16	31.2	56.3
No. gen'l. sulf.....	48	6.3	8.3	6	33.3	16.7	3	66.7	33.3
Local sulf.....	93	10.7	17.2	21	33.3	42.9	14	28.6	57.1
No local sulf.....	69	5.8	5.8	6	33.3	16.7	5	60.0	40.0

TABLE VIII

SHOWING THE NUMBER OF CASES YIELDING *Clostridium welchii* IN THE DÉBRIDED TISSUE, THE NUMBER IN WHICH THIS ORGANISM PERSISTED AND THE NUMBER OF CASES IN WHICH THIS ORGANISM APPEARED AS A NEW CULTURE, WITH AND WITHOUT SULFONAMIDE TREATMENT

Soft-Part Wounds—682

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser.	Triv.		Ser.	Triv.		Ser.	Triv.
Clostridium Welchii.....	97	8.2	17.5	10	40.0	20.0	6	33.3	33.3
Gen'l. sulf.....	75	10.7	16.0	10	40.0	20.0	6	33.3	33.3
No. gen'l. sulf.....	22	0	22.7	0	0	0	0	0	0
Local sulf.....	67	10.4	16.4	9	44.4	22.2	6	33.3	33.3
No local sulf.....	30	3.3	20.0	1	0	0	0	0	0

TABLE IX

SHOWING THE NUMBER OF CASES YIELDING ANAEROBIC COCCI IN THE DÉBRIDED TISSUE, THE NUMBER IN WHICH THESE ORGANISMS PERSISTED AND THE NUMBER OF CASES IN WHICH THESE ORGANISMS APPEARED AS NEW CULTURES, WITH AND WITHOUT SULFONAMIDE TREATMENT

Soft-Part Wounds—682

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser.	Triv.		Ser.	Triv.		Ser.	Triv'
Anaerobic Cocci.....	70	7.2	12.9	5	60.0	20.0	3	33.3	66.7
Gen'l. sulf.....	40	5.0	10.0	4	50.0	25.0	3	33.3	66.7
No. gen'l. sulf.....	30	10.0	16.7	1	100.0	0	0	0	0
Local sulf.....	35	5.7	11.4	4	50.0	25.0	3	33.3	66.7
No local sulf.....	35	8.6	14.3	1	100.0	0	0	0	0

The bacteriology has been interesting and important. We must remember that these are almost always mixed cultures and bacterial synergisms and antagonisms may play an important rôle but certain organisms stand out as most important, namely the hemolytic streptococcus, the coagulase-positive staphylococci, the pathogenic gram-negative bacilli, the Welch bacillus and the anaerobic cocci. These were found in the débrided tissues in many cases but in the great majority they did not persist, being removed either by the operative procedures or by the local defenses of the body or by both. However, in many instances organisms of these same groups appeared in later cultures in cases in which they were not originally found. These may have been there originally and were not recovered, but the chances are that they often represented secondary contamination occurring during the course of treatment, particularly in open compound fractures and burns. We were anxious to find out whether the sulfonamides would eliminate the organisms found in the débrided tissue and prevent secondary contamination and infection, but such was not the case. There was no greater reduction of the original contamination nor of the secondary contamination in the drug treated cases than in the controls which received no drug.

COMPOUND FRACTURES

In discussing the results in compound fractures it should be clearly understood that we have only considered this problem from the point of view of infection. It is recognized that a compound fracture has two elements, namely, the break in the bone and the wound of the surrounding soft parts and skin. The end-result desired is a normally functioning member, with firm bony union and freely contracting muscle around the bone and freely moving joints on either end of the fractured bone. This end-result is materially altered or delayed by infection within or around the bone or by infection in the soft parts. Infection is more likely to occur and is much more serious when it develops in a compound fracture than when it develops in a soft-part wound. Bone is less resistant to infection than soft parts and it is frequently cut off from its blood supply either as a loose fragment or as the exposed end of the shaft which has been stripped of its periosteum. Infection may either develop at once, within the first few days after the injury, or start up with the first efforts to obtain full motion of the part, or lie dormant for months after the wound has apparently healed and suddenly or gradually develop after some trauma or some general lowering of resistance.

In this series the compound fractures have been grouped in many different ways according to the common factors and, while in every category there are other factors at work beside the common factor, this seems to be the only way in which the significance of these factors can be determined.

TABLE X

PERCENTAGE OF INFECTION IN COMPARABLE GROUPINGS IN 471 COMPOUND FRACTURES

	Totals	% Infected	
		Serious	Trivial
Major fracture	275	14.2	8.0
Minor fracture	196	8.2	12.7
Shock	112#	19.6*	8.0
No shock	354#	9.3*	10.7
Maximum contamination	234	16.7*	8.5
Minimum contamination	237	6.8*	11.4
Maximum tissue damage	360	13.6*	11.1
Minimum tissue damage	111	5.4*	6.3
Wound left open	91#	16.5*	11.0
Partial closure	73#	19.2*	11.0
Complete closure	304#	8.6*	9.5
Fracture plated	54#	27.8	9.3
Plaster immobilization	215#	14.0	6.5
Skeletal traction	62#	17.7	9.7

Data incomplete.
* Statistically significant.

We find that shock, maximum gross contamination and maximum tissue damage are associated with the most serious infections. Early operation, complete wound débridement and prolonged wound washing do not appear to play as important rôles as with soft-part wounds. The incidence of serious infections, when the wounds are closed completely, is less than when the wounds are left open or are partially closed. This has been a consistent finding throughout the study and it seems to be reasonably explained when we consider that wounds which are left open, with fractured bone exposed, are subject to secondary contamination over a fairly long period of time before the bone has had a chance to grow a protective covering of granulation tissue.

TABLE XI

INCIDENCE OF INFECTION IN DRUG-TREATED CASES AND IN COMPARABLE CONTROLS IN 471 COMPOUND FRACTURES

	Totals	% Infected	
Local sulfanilamide and sulfadiazine in equal parts	145		
Serious infection	18	12.4	
Trivial infection	26	17.9	30.3
Local sulfanilamide	172		
Serious infection	20	11.6	
Trivial infection	11	6.4	18.0
Total local sulfonamide	225		
Serious infection	41	12.6	
Trivial infection	37	11.4	24.0
No local sulfonamide	141		
Serious infection	14	9.9	
Trivial infection	7	5.0	14.9
Total general sulfonamide	359		
Serious infection	47	13.1	
Trivial infection	38	10.6	23.7
No general sulfonamide	112		
Serious infection	8	7.1	
Trivial infection	9	8.0	15.1
General without local sulfonamide	38		
Serious infection	6	15.8	
Trivial infection	2	5.3	21.1

The combined local and general, or the general, use of sulfonamides alone have not lowered the incidence of local infection. Although there

TABLE XII

COMPOUND FRACTURES

Total 471 — Deaths from Infection, 2.

	Case I	Case II
Bones	Tibia, fibula, ilium.	Femur, tibia and fibula.
Operation	Partial closure without tension. Plaster.	Partial closure with tension. Plate.
Primary drug	Local sulfanilamide General sulfadiazine	Local sulfanilamide. General sulfadiazine
Day of death	9th	110th
Principle organisms	Coag.-pos. staph., green strept., *Cl. bifermentans*	Coag.-pos. staph., *E. coli*, *B. proteus*, *B. pyocyaneus*, *Cl. sporogenes*.

Cases requiring, because of infection:

(a) Excision of dead tissue	5
(b) Wound to be opened for drainage	11
(c) Incision for drainage	15
(d) Amputation	16

are only two cases which died as a result of infection, and these yielded no positive blood cultures, a fair number of cases needed secondary surgical procedures because of wound infection—5 required excision of dead tissue, 11 had to have wounds opened up, 15 required a new incision for drainage of abscesses, and 16 needed secondary amputation. The two fatal cases both had local as well as general prophylactic sulfonamide therapy.

TABLE XIII

SHOWING THE NUMBER OF CASES YIELDING HEMOLYTIC STREPTOCOCCUS IN THE DÉBRIDED TISSUE, THE NUMBER IN WHICH THIS ORGANISM PERSISTED AND THE NUMBER OF CASES IN WHICH THIS ORGANISM APPEARED AS A NEW CULTURE, WITH AND WITHOUT SULFONAMIDE TREATMENT

Compound Fractures—471

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser.	Triv.		Ser.	Triv.		Ser.	Triv.
Hemolytic Strep	34	20.6	17.6	8	37.5	25.0	17	35.3	23.5
Gen'l. sulf	24	29.1	20.8	7	52.9	28.6	14	28.6	21.4
No gen'l. sulf	10	0	10.0	1	0	0	3	66.7	33.3
Local sulf	18	22.2	27.8	4	0	50.0	13	23.1	23.1
No local sulf	16	18.8	6.2	4	75.0	0	4	75.0	25.0

TABLE XIV

SHOWING THE NUMBER OF CASES YIELDING COAGULASE-POSITIVE *Staphylococcus aureus* IN THE DÉBRIDED TISSUE, THE NUMBER IN WHICH THIS ORGANISM PERSISTED AND THE NUMBER OF CASES IN WHICH THIS ORGANISM APPEARED AS A NEW CULTURE, WITH AND WITHOUT SULFONAMIDE TREATMENT

Compound Fractures—471

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser.	Triv.		Ser.	Triv.		Ser.	Triv.
Coag.-pos. *Staph. Aureus*	41	12.2	19.5	12	33.3	50.0	36*	44.5	21.8
Gen'l. sulf	32	12.5	25.0	11	27.3	54.6	33	42.4	30.3
No. gen'l. sulf	9	11.1	0	1	100.0	0	3	66.7	0
Local sulf	30	10.0	26.6	10	20.0	60.0	33	42.4	30.3
No local sulf	11	18.2	0	2	100.0	0	3	66.7	0

TABLE XV

SHOWING THE NUMBER OF CASES YIELDING PATHOGENIC GRAM-NEGATIVE AEROBIC BACILLI IN THE DÉBRIDED TISSUE, THE NUMBER IN WHICH THESE ORGANISMS PERSISTED AND THE NUMBER OF CASES IN WHICH THESE ORGANISMS APPEARED AS NEW CULTURES, WITH AND WITHOUT SULFONAMIDE TREATMENT

Compound Fractures—471

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser.	Triv.		Ser.	Triv.		Ser.	Triv.
Pathogenic Gran.-neg.									
Aerobic Bacilli	78	23.1	11.5	12	50.0	25.0	28	28.6	25.0
Gen'l. sulf.	58	27.6	10.3	7	85.7	0	19	31.6	26.3
No gen'l. sulf.	20	10.0	15.0	5	0	50.0	9	22.2	22.2
Local sulf.	54	26.0	9.3	6	83.3	0	18	33.3	22.2
No local sulf.	24	16.7	16.7	6	16.7	50.0	10	20.0	30.0

TABLE XVI

SHOWING THE NUMBER OF CASES YIELDING *Clostridium welchii* IN THE DÉBRIDED TISSUE, THE NUMBER IN WHICH THIS ORGANISM PERSISTED AND THE NUMBER OF CASES IN WHICH THIS ORGANISM APPEARED AS A NEW CULTURE, WITH AND WITHOUT SULFONAMIDE TREATMENT

Compound Fractures—471

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser.	Triv.		Ser.	Triv.		Ser.	Triv.
Clostridium Welchii	90	21.1	11.1	11	45.5	0	6	33.3	16.7
Gen'l, sulf.	68	22.1	13.2	11	45.5	0	4	25.0	25.0
No gen'l. sulf.	22	18.2	4.3	0	0	0	2	50.0	0
Local sulf.	61	19.7	13.1	9	33.3	0	3	33.3	33.3
No local sulf.	29	24.1	6.9	2	100.0	0	3	33.3	0

TABLE XVII

SHOWING THE NUMBER OF CASES YIELDING ANAEROBIC COCCI IN THE DÉBRIDED TISSUE, THE NUMBER IN WHICH THESE ORGANISMS PERSISTED AND THE NUMBER OF CASES IN WHICH THESE ORGANISMS APPEARED AS A NEW CULTURE, WITH AND WITHOUT SULFONAMIDE TREATMENT

Compound Fractures—471

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser.	Triv.		Ser.	Triv.		Ser.	Triv.
Anaerobic Cocci	55	3.6	14.5	3	0	33.3	6	33.3	16.7
Gen'l. sulf.	41	4.9	17.1	3	0	33.3	4	25.0	0
No. gen'l. sulf.	14	0	7.1	0	0	0	2	50.0	50.0
Local sulf.	32	6.2	21.9	3	0	33.3	4	25.0	0
No local sulf.	23	0	4.3	0	0	0	2	50.0	50.0

With regard to the bacteriology it is seen that there is a higher proportion of cases yielding hemolytic streptococci, coagulase-positive *Staphylococcus aureus* and *Cl welchii* than in the soft-part wounds and, furthermore, that they more often persisted and more often appeared as new cultures. The pathogenic gram-negative aerobes did not appear as often initially but appeared anew in a much higher percentage in compound fractures than in soft-part wounds. The sulfonamides did not particularly favor their elimination or prevent their secondary development in the wounds.

BURNS

The infection rate in burns is very disturbing, particularly in deep second and third degree cases.

TABLE XVIII

PERCENTAGE OF INFECTION IN COMPARABLE GROUPING IN 347 BURNS

	Totals	% Infected	
		Serious	Trivial
Second degree	192	10.4*	14.1*
2nd and 3rd degree	155	30.3*	34.2*
Area < ten per cent	180#	10.0*	23.2
Area > ten per cent	166#	28.9*	22.9
Shock	45#	40.0*	13.3
No shock	292#	15.8*	23.3
Maximum contamination	154	27.3*	27.3
Minimum contamination	193	12.4*	19.7
Maximum tissue damage	213#	23.0*	27.7
Minimum tissue damage	131#	12.2*	16.0
Minimum washing	156	11.5*	22.4
Maximum washing	191	25.1*	22.6

Data incomplete.
* Statistically significant.

As with the other groups of cases, the extent of the involved area, the depth of the injury, the intensity of gross contamination and tissue damage run parallel with the percentage of infections.

TABLE XIX

PERCENTAGE OF INFECTION OCCURRING WITH VARIOUS FORMS OF TREATMENT IN 347 BURNS

	Totals	% Infected	
		Serious	Trivial
Tannic acid without sulfonamide	20#	30.0	35.0
Quebracho-tannin	11#	54.5	18.2
Tannic acid with sulfonamide	23#	21.7	26.1
Compression dressings	81#	13.6	21.0
Zinc peroxide with pressure	15#	0	20.0
Saline compresses with pressure	34#	14.7	20.6
Total sulfadiazine ointment	65#	15.4	29.3
Total sulfadiazine spray	37#	5.4	29.7
Total sulfonamide film	16#	31.3	25.0
Total sulfonamide powders	31#	45.2	3.2
Total local sulfonamides	172#	20.9	23.8
General sulfadiazine	141#	31.2	19.9
No general sulfadiazine	201#	10.4	24.9

Data incomplete.
* Statistically significant.

The methods of treatment have varied considerably and great latitude has been granted the different units to explore new fields of burn therapy. The compression dressing method has stood out as representing the greatest proportion of right principles and the lowest incidence of infection. The initial dressing containing a bacteriostatic agent has a slight but not clear-cut superiority over the simple nonadherent ointments.

In burns we have a tissue extensively damaged which may contain sulfonamide inhibitors. There is evidence that there may be greater or less absorption of the drugs from burned surfaces according to the vehicle in which the sulfonamide drugs are contained. The ideal vehicle has not yet been found. Many are being tried. The local drug action may be inhibited while the general effect may be obtained from local applications.

There were only two burn deaths in which infection played an important rôle and these were so extensive that they might have died without infection. Both had local and general sulfonamide treatment.

TABLE XX

BURNS

Total 347	Deaths from Infection, 2.	
	Case I	Case II
Degree	2nd and 3rd	2nd and 3rd
Region	Face, trunk, both arms and hands, right leg.	Face, trunk and all limbs.
Per cent of body	60–70	60-70
Local Rx	Equal parts powder sulfanilamide and sulfadiazine.	Fibrinogen, thrombin, sulfadiazine.
General Rx	Sulfadiazine	Sulfadiazine
Day of death	5th	28th
Principle organisms	Coag.-pos. staph., nonhemolytic strept., *B. pyocyaneus*, *B. proteus*.	Coag.-pos. staph.,hemolytic strept. (Group D), *B. pyocyaneus*, *E. coli*.

TABLE XXI

SHOWING THE NUMBER OF CASES YIELDING HEMOLYTIC STREPTOCOCCI IN THE DÉBRIDED TISSUE, THE NUMBER IN WHICH THIS ORGANISM PERSISTED AND THE NUMBER OF CASES IN WHICH THIS ORGANISM APPEARED AS A NEW CULTURE, WITH AND WITHOUT SULFONAMIDE TREATMENT

Burns—347

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser.	Triv.		Ser.	Triv.		Ser.	Triv.
Hemolytic Strep.	48	25.0	22.9	12	50.0	25.0	34	47.1	47.1
Gen'l. sulf.	28	32.1	21.4	6	66.7	33.3	13	76.9	23.1
No gen'l. sulf.	20	15.0	25.0	6	33.3	16.7	21	28.6	61.9
Local sulf.	29	31.0	20.7	5	60.0	40.0	12	33.3	66.7
No local sulf.	19	15.8	26.3	7	42.9	14.3	22	54.5	36.4

TABLE XXII

SHOWING THE NUMBER OF CASES YIELDING COAGULASE-POSITIVE *Staphylococcus aureus* IN THE DÉBRIDED TISSUE THE NUMBER IN WHICH THIS ORGANISM PERSISTED AND THE NUMBER OF CASES IN WHICH THIS ORGANISM APPEARED AS A NEW CULTURE, WITH AND WITHOUT SULFONAMIDE TREATMENT

Burns—347

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser.	Triv.		Ser.	Triv.		Ser.	Triv.
Coag.-pos. *Staph. Aureus*	51	21.6	31.4	25	32.0	44.0	52*	38.5	38.5
Gen'l. sulf.	18	38.9	16.7	11	54.5	18.2	29	55.2	24.1
No. gen'l. sulf.	33	12.1	39.4	14	14.3	64.3	23	17.4	56.5
Local sulf.	28	21.4	32.1	13	30.8	46.1	31	38.7	38.7
No local sulf.	23	21.7	30.4	12	33.3	41.7	21	38.1	38.1

TABLE XXIII

SHOWING THE NUMBER OF CASES YIELDING PATHOGENIC GRAM-NEGATIVE AEROBIC BACILLI IN THE DÉBRIDED TISSUE, THE NUMBER IN WHICH THESE ORGANISMS PERSISTED AND THE NUMBER OF CASES IN WHICH THESE ORGANISMS APPEARED AS A NEW CULTURE, WITH AND WITHOUT SULFONAMIDE TREATMENT

Burns—347

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser.	Triv.		Ser.	Triv.		Ser.	Triv.
Pathogenic Gram-neg. Aerobic Bacilli	82	24.4	23.3	24	50.0	33.3	51	45.1	27.5
Gen'l. sulf.	43	37.2	18.6	16	56.2	25.0	28	53.6	28.6
No. gen'l. sulf.	39	10.2	28.2	8	37.5	50.0	23	34.8	26.1
Local sulf.	44	29.5	25.0	12	58.3	33.3	21	52.4	19.0
No local sulf.	38	18.4	21.1	12	41.7	33.3	30	40.0	33.3

The bacteriologic studies reveal that many of the hemolytic streptococci persist in the burned area or come in as new contaminants in the face of local as well as general sulfonamide therapy. The staphylococci are the most numerous of the pathogens in the persistent and new cultures, but the gram-negative aerobic bacilli, particularly the *E. coli, B. pyocyaneus* and *B. proteus* groups, run the staphylococci a close race. If the problem of infection in burns is to be solved it must be concerned with all of these groups of organisms. Something must be sought for which will be effective in halting the growth of these organisms in the presence of the dead and damaged tissue of burns.

CONCLUSIONS

(1) Our studies have indicated the important factors concerned in the development of infection in accidental contaminated wounds and burns.

(2) We have found that the sulfonamides minimize the general spread of infections and cut down the incidence of septicemia and death.

(3) We have no evidence that they lessen the incidence of local infection when used as we have employed them.

(4) If we are going to lessen the incidence of local infection in war wounds and burns, some other forms of the sulfonamides or some other bacteriostatic agents must be found which will be effective against the contaminating organisms in the presence of damaged tissue.

DISCUSSION.—DR. EVARTS GRAHAM (St. Louis, Mo.): When the Committee on Surgery of the National Research Council was organized, in the spring of 1940, one of the questions which was put to it by the Surgeon-Generals of the Army and Navy was: "What about the use of sulfonamides in battle casualties, in wounds?"

Shortly before this, the report of Jensen had come out about the beneficial effect, as he thought, on compound fractures of the use of sulfanilamide applied locally. In order to answer this very important question, and in order to remove impressions and emotions and other nonscientific factors as much as possible from the study, the subcommittee, of which Dr. Frank Meleney has been chairman, was formed, with the idea of making as satisfactory and as closely observant a study of the effect of sulfonamides on wounds which simulated battle casualties, as possible.

Now the result of this study, which was somewhat later in getting started than we had hoped that it would be because of various reasons, has, nevertheless, I think been brought to rather satisfactory conclusions which you have heard today. I say satisfactory, only from the standpoint of the fact that the study has been made most carefully by a considerable number of very competent observers, whose names have been mentioned to you.

It is unsatisfactory, in the sense that it was disappointing, especially after the enthusiastic reports of the success of sulfonamides applied locally, particularly sulfanilamide, in the wounds at Pearl Harbor. I think almost everyone was led to believe that, after all, now we have a panacea which might even perhaps minimize the necessity of surgical asepsis. That is certainly not the case. The day of listerism is not yet gone. The sulfonamides will not replace surgical asepsis.

I feel that you who have not been closely associated with this work perhaps can hardly appreciate the enormous amount of labor which has gone into it. There is no other comparable study of the effect of sulfonamides on wounds anywhere in the world. There is nothing that begins to compare with the carefulness with which this study has been made. I feel that everyone, not only the American Surgical Association

and the Surgeon-Generals, but everyone, should be greatly indebted to this committee who have worked so hard for so long a period in arriving at these results which seem to be very dependable. Emotions and impressions have been eliminated, and only hards facts have been retained.

Dr. John S. Lockwood (Philadelphia) : I am sure that all of the collaborators would join with me in expressing here our great appreciation for the enormous amount of labor which Dr. Meleney, in particular, has expended on this study. In his responsibility, he has not only had supervision of one of the major units in the project, but he also has carried the main burden for collecting and tabulating all of these statistics. The conclusions which he has presented here today are, I believe, joined in unanimously by the Subcommittee on Surgical Infections and by the other investigators.

It might be said that Dr. Meleney has set an exceedingly high standard. From the very beginning he has expressed unwillingness to be satisfied with anything other than complete prevention of infection in traumatic wounds. I think all of us have hoped that that ideal might be closely approximated, but as time has gone on, we have become increasingly aware of the fact that no measure designed simply to deal with bacteria in wounds is likely completely to achieve this high ideal, unless, of course, an agent could be found which would destroy all of the contaminating bacteria.

In accounting for the failures of sulfonamide, several observations might be appropriate: First, as Dr. Meleney pointed out, these infections were not for the most part, systemic, invasive infections. They were local, and the area involved in the infection in the majority of cases was closely delimited to the area of the wound. Furthermore, most of the infections—at least those that occurred in the project under my supervision—were delayed. They did not show up as acute fulminating infections, but appeared five, seven, or eight days after wound closure. The infections were most common in those wounds in which delayed healing might have been expected by reason of poor adjustment of physiologic factors. I am reminded of Arey's important monograph on wound healing, in which, after pointing out the three main phases of wound healing, namely, the refractory stage, the destructive stage, and the reparative stage, he states that the critical stage of wound repair from the standpoint of infection is the *destructive* stage; and the infections that occurred in spite of sulfonamides were those that developed during the destructive phase. The factors which encouraged bacterial activity were retention of products of tissue injury, tension, and incomplete obliteration of dead space.

Furthermore, the very same factors which will tend to delay healing and complicate the wound repair, are also factors which tend to inhibit sulfonamide action. Perhaps we cannot find an ideal sulfonamide. If we find a drug which, on the one hand, will not produce local foreign body reaction but will disappear from the wound, that particular drug will not be active after five, six, or seven days—the time at which many of these infections develop. In all probability we will not be able with sulfonamides to eliminate the infections which develop because of poor physiologic adjustments in the wound. We cannot expect any more of the sulfonamides than that they will delay bacterial growth under conditions where their action is not inhibited. Therefore, the outcome of this study certainly justifies a continuing recognition of the predominant importance of surgical management and of physiologic factors in relation to wound healing and wound infection. At the same time, it points out the fact that the problem of deaths from infection in traumatic wounds should be very significantly minimized with sulfonamides.

Nothing that has been said about the lack of effectiveness of sulfonamides under the conditions used in this clinical experiment, should contradict the wisdom of the practice of employing sulfonamides routinely in battle casualties, during the period between injury and the time the casualty reaches the hospital for definitive treatment. The problem there is different from the problem which we studied in these wound study projects, and if the multiplication of bacteria in the wound fluids can be delayed for even a few hours during the transport of the wounded subject from the field of injury to the hospital, that should significantly reduce the likelihood of postoperative infection. This is entirely beside the point of whether or not sulfonamides should be used in the wound if, and when, the wound is closed.

We have plenty of evidence to support the wisdom of the directive, both in the

Army and in the Navy, against routine closure of traumatic wounds. If any of us needed to learn the wisdom of that decision, I think we have the evidence.

Finally, there remains every reason to believe that sulfonamide therapy properly used in cases with established infections will be definitely of value, and we now have in penicillin what appears to be an even more powerful weapon in dealing with staphylococcic and *Clostridium welchii* infections.

DR. MARTIN B. TINKER (Ithaca, N. Y.): Wound excision in contraindication to débridement in connection with the treatment of infected wounds has not been given the attention it seems to deserve today. On January 27, 1909, the Medical Society of the State of New York had a symposium on fractures, participated in by Drs. Harvey Cushing, Lewis Stimson, and Charles Scudder, in which I, as a young surgeon, at that time, presented a paper on contaminated compound fractures. At that session I proposed the excision of wounds, for removal of contaminated areas, without injuring important structures. Damaged areas were outlined by packing the wound first with gentian violet and pure carbolic acid; the wound was then excised, avoiding great vessels, nerves, and other important structures.

The case of a brakeman on the New York Central Railroad, who stepped in front of a slowly moving freight car loaded with brick to set the brakes, was reported. This man slipped, fell with his arm across the rail, and the loaded car passed over his arm, crushing the humerus and seriously contaminating the wound. He has a useful arm, and, although he has a flail joint, he is working for the Eastman Kodak Company, in Rochester, N. Y., at the present time. This man was demonstrated in Brooklyn, at the Academy of Medicine.

Another instance. A farmer was brought to me, whose patella was fractured by the kick of a horse. The knee joint was opened, and was contaminated with horse manure. The wound was disinfected and stained, and the wound excised and closed. The man recovered perfect use of his knee.

For experiments, the Department of Physiology, at Cornell University, gave me animals which they had chloroformed and sacrificed. Various wounds, which were definitely contaminated by resistant bacterial cultures. The wounds were excised after packing with staining and disinfecting gauze. Sections taken, and bacteriologic cultures, were proved free of contamination. These cases, with others, were also reported after World War I, at the meeting of the Military Surgeons at New Orleans, April 22-24, 1920.

The more thorough method of wound excision antidates débridement, as used by La Maitre, several years. No other method has excelled the results of wound excision for serious injuries.

DR. J. ALBERT KEY (St. Louis, Mo.): I do not know where it is—it may be the unwieldiness of the series, or it may be in the punch-card system—but there is something wrong somewhere. I am perfectly convinced, and this is not emotion, that any report of a series of cases which concludes that the rational implantation of sulfonamides in contaminated wounds after they have been properly débrided does not lower the incidence of infection in these wounds, is wrong, provided the débridements and the after treatment are equivalent.

This is a monumental piece of work, backed by a lot of able observers, but I think that a few years from now they will be ashamed of their conclusions.

DR. FRANK L. MELENEY (New York City, closing): I am glad to have Doctor Lockwood's assurance that the other members of the Committee and the other responsible investigators approve the presentation of the results and the conclusions which we have drawn. I might also say that I think we would all approve of his additional remarks.

With regard to Doctor Tinker's observations, I would say that the basic surgical procedure which we determined upon in the beginning, was that the wounds should be, as far as possible, excised, and that is the meaning of the word "débridement" as we have used it in this paper. Of course, in many cases this had to be compromised, for one reason or another, to preserve important structures, such as blood vessels and nerves, or when, for one reason or another, an unsatisfactory or incomplete excision had to be resorted to.

With regard to Doctor Key, I can only say that in our group, at the beginning of the study, we had those who sincerely believed (and I might say that we all hoped), that these drugs would materially cut down the incidence of infection. There was no one in the group who was prejudiced against them. We were simply seeking to find out the facts, and we were not trying to prove anything.

I believe that our whole group has come to this consensus of opinion. We all believe that these figures do represent facts and tell the truth.

I greatly appreciate Doctor Graham's favorable comments. I would like to state that without the hearty support of his Committee on Surgery, this project would never have been initiated or carried forward. I believe that it is only fair to report at this time that we all feel that the most efficient unit in this study has been the one carried on here in Cincinnati by our good friends Mont Reid and William Altemeier.

BASIC PRINCIPLES IN THE TREATMENT OF THERMAL BURNS*

ALLEN O. WHIPPLE, M.D.
NEW YORK, N. Y.

FROM THE DEPARTMENT OF SURGERY, COLUMBIA-PRESBYTERIAN MEDICAL CENTER, NEW YORK, N. Y.

GLOBAL MECHANIZED WARFARE on land, sea, and in the air has resulted in an unprecedented number of thermal burns; with a demand for an immediate answer to the confused and very debatable question of how best to treat them. This general disagreement in all the combatant countries regarding the best therapy, both as first aid and definitive, is the result of a number of factors.

I: The failure, on the part of physicians and surgeons, to understand the underlying pathology and disturbed physiology of the burned individual, and the differences in the wound caused by a burn and soft-part wounds. II: The failure of those reporting the results of various types of local treatment to differentiate between the burns with superficial skin damage, so-called second degree burns, and burns resulting in areas with total skin destruction, or third degree burns. The second degree burn will heal with any form of local treatment provided the burned area is protected from contamination and the local application does not destroy the remaining epithelial covering. The latter, or third degree burn, will not heal without a prolonged period of granulation after separation of slough, and slow epithelial spread resulting in contracting scars—unless this period is shortened by skin grafting at the earliest favorable time. Infection, sepsis, hypoproteinemia and anemia are common to all untreated, or improperly treated, extensive third degree burns. Third degree and mixed second and third degree burns are the real therapeutic problems and are the criteria by which every therapy should be judged. III: Failure to appreciate the importance of trained and experienced groups of individuals interested in the care of burned patients. Special experience is expected of surgeons dealing with lesions of the various systems, but the treatment of burns in the majority of hospitals is left to inexperienced interns or residents, or to the least experienced of the Junior Attendings. The Burn Committees in England, Canada and the United States are unanimous in emphasizing the importance of well-organized "burn teams" in the care of burn casualties, especially if many such cases are to be cared for in military or civilian hospitals. By burn team we mean a group made up of a general surgeon, interested in problems of infection and wound healing, a physician or technician, thoroughly trained in problems of fluid, protein and electrolyte imbalance, a general plastic surgeon—not an oral or faciomaxillary specialist—with experience in skin grafting large granulating areas, a group of trained nurses and orderlies, able and willing to stand the stress and strain of caring for severely burned patients.

* Read before the American Surgical Association, May 14, 1943, Cincinnati, Ohio.

IV: The failure to appreciate the importance of "timing" in the sequence of events in the pathogenesis, symptomatology and treatment of severely burned patients. Dr. Fraser Gurd has so properly and repeatedly emphasized this most important factor in the study and treatment of burns. V: The one outstanding contribution to burn therapy in preventing and combatting shock is the accepted use of plasma instead of salt solution and whole blood. This has reduced the mortality of burn casualties, but has saved many severely burned cases, with their late and difficult problems of treatment, which formerly died in the first day or two after the injury. Late morbidity associated with anemia, hypoproteinemia, nitrogen loss with emaciation are some of the newer aspects of late survivals and will be discussed by Doctor Lund and Doctor Allen.

VI: The introduction of sulfonamide therapy in the treatment of burns has caused more confusion than benefit, because by so many it was looked upon, hopefully but unintelligently, as a panacea. These drugs, given systemically, have undoubtedly controlled, if not eliminated septicemia and bacteriemia in severe burns. But the local use of the sulfonamides has not fulfilled the early promise, and the benefits of these amazing drugs will depend upon finding their optimum ionization and p_H in proper media when used with sound surgical principles and with due consideration of the underlying pathology of the burned areas.

Wounds resulting from burns differ from soft-part wounds in many respects. As a rule they are more extensive; cause more damage to the important protecting tissue, the skin; expose a greater surface area to contamination. But this injured surface is at first sterilized by the heat producing the burn and offers a better opportunity for protection from contamination if prompt and intelligent means are used to provide a protective covering over the burned surface in the initial treatment. In the severe burns, with areas of total destruction of the skin, gangrene of tissue takes place which has to be sloughed off before repair by granulation and epithelization can occur. If these areas are extensive, the patient develops infection, anemia, hypoproteinemia and nitrogen imbalance that is seen in any extensive process of repair following extensive gangrene of tissue.

The edema of, and absorption from, a burned area differs from a soft-part wound or injury in a very interesting manner. The studies of Drinker,[1, 2] and his associates, and of McMaster,[3, 4] have recently established experimental evidence of great importance both from the standpoint of pathogenesis and therapy. In experimentally produced burns it has been shown that there is a very marked increase in the capillary permeability in the periphery of the burned area as well as in the rate of lymph flow away from this zone. But of greater importance, Drinker has shown that there is a marked delay in the production or liberation of thromboplastic substance in the burned area as compared with that found in crushed tissue or soft-part wounds. What the cause of this delay is, is only conjectural. Does the heat of the burn affect the thermolabile thromboplastic substance?

Is it because the normally present preenzyme is destroyed and subsequently is brought to the area from other parts of the body?

It is only after eight to ten hours that the lymph flow from a burned area begins to slow down as a result of coagulation of the blood and lymph in the injured tissue. Were it not for this excessive flow of lymph and interstitial fluid away from the area, *i.e.*, fluid which has left the hyperpermeable capillaries to go into the intercellular spaces, a very much more marked edema of the burned area would take place. Drinker has demonstrated this by the immediate blocking of lymph drainage from a dog's paw, that has been placed in boiling water for two minutes, by injecting muscle extract into the burned area. The lymph recovered from a burned area has been shown to contain a strong vasoconstrictor substance. Studies by Drinker, and his associates, and by Alrich and Lehman, as yet unpublished, have demonstrated this vasoconstrictor substance in high dilutions. May this not be a definite cause of the secondary shock that appears in extensive burns within the first ten hours after receipt of the burn?

This increased lymph flow from the burned area for the first few hours after the receipt of the burn is of great significance in the delayed localization of infection which follows contamination of a burned surface and emphasizes the importance of taking every precaution against early contamination, especially by the hemolytic streptococcus and staphylococcus usually spread from the unsterile hands and unmasked noses and throats of those applying the initial protective dressings.

Drinker has also demonstrated that if an animal's paw, after such an exposure to boiling water, is immediately encased in a plaster of paris jacket, the edema does not take place and the lymph flow is markedly decreased as the result of this lack of edema. This, of course, means a great reduction in the plasma loss from capillary leakage into interstitial tissue spaces, and a corresponding lack of shock due to plasma loss. Gangrene of the tissues is far less in the plaster-encased paw than in the control with unbandaged paw. These studies explain the efficacy of firm pressure dressings that has been so ably emphasized by Allen and Koch,[5] Siler,[6] Owens,[7] and others, and that, as a basic method of treatment is coming to be more generally accepted.

Considering these essential characteristics of the pathology of burns, the basic and simple principles of therapy may be summed up as follows: The most important early general complication is plasma volume loss as a result of plasma leakage into the interstitial spaces. This can be largely prevented by firm pressure bandaging and controlled by plasma transfusion. The prevention and treatment of shock in every severe burn, superficial or deep, is the first indication and should precede any definitive treatment. The most important local complication is infection. Inasmuch, as the burned surface is initially sterile, every precaution should be taken to prevent contamination. This can be accomplished for the most part, by adequate masking of nose and mouth and surgical asepsis in applying the initial dressings and by

leaving the wound undisturbed thereafter unless infection is evident. This initial dressing should be a fine-meshed gauze or tulle gras, impregnated with or covering a bland simple ointment or solution that will not damage the remaining epithelium. The subsequent dressings, provided the above precautions have been used, will depend upon the degree of skin damage. If total skin destruction has occurred, dressings to favor the removal of the slough as soon as possible, with skin grafting of the entire denuded granulating area at the earliest favorable time, are the essential considerations. Any form of treatment in these total skin burns which tends to seal in infection and causes a delay in skin grafting is to be wholly condemned. Here, more than in any other type of burn, proper timing is the secret of success.

In estimating the relative efficacy of any new or old treatment for burns, it is not the results in superficial burns but in total skin burns that should be the criterion. To date, some eighty methods of burn therapy have been published. Very few of the authors reporting their results have been intelligent or careful enough to classify their cases accurately. The studies now going on in the several Burn Projects, under the National Research Council will, when assembled and analyzed, give invaluable pathologic, bacteriologic and therapeutic data on this very important but controversial subject.

There are a number of new and old methods of local treatment that are being carefully studied in the clinics where these Burn Projects are functioning. These include the sulfonamide creams and ointments, films of several kinds, with and without sulfonamides, the use of the paraffin spray, and ultracentrifuged, finely divided particles of clay, known as bentonite, made into water-soluble colloidal gels. Some of these preparations, when used with an understanding and appreciation of the basic principles of burn therapy, will undoubtedly prove valuable.

Of the dozens of proprietary preparations, especially those with exaggerated and fantastic therapeutic claims, the less said the better. The free advertising that some of these have been given in popular magazines is inexcusable and unfortunate, for, as always, they misinform the ignorant but innocent public.

There are a number of new and fundamentally important problems that, with further study, will undoubtedly modify and improve the treatment of the burned patient. One of these is the problem of nitrogen imbalance that is being discussed by Doctor Lund. Another is the discovery of a fluid containing protein and electrolyte, of proper molecular make-up, that can be used as a substitute for plasma, with all its advantages. Recent experimental work in oral sodium therapy by Rosenthal[8] promises interesting results in clinical cases, but there are many phases of this subject, such as the relation of serum protein loss to sodium loss and intake that need much more study before the experimental results in animals can be correlated with clinical results.

Certainly, the therapy of burns is only beginning to be understood, and

because of the great and urgent interest in the subject, much progress will be made before the war is over.

REFERENCES

1 Drinker, C. K., Glenn, W. W. L., and Peterson, D. K.: The Flow of Lymph from Burned Tissue; With Particular Reference to the Effects of Fibrin Formation upon Lymph Drainage and Composition. Surgery, **12**, No. 5, 685–693, November, 1942.

2 Glenn, W. W. L., Muus, J., and Drinker, C. K.: Observations on the Physiology and Biochemistry of Quantitative Burns. In press, to appear in May, 1943, issue of Jour. Clin. Inv.

3 McMaster, P. D.: Lymphatic Participation in Cutaneous Phenomena. The Harvey Lectures, Series XXXVII, 227–268, 1941–42.

4 McMaster, P. D., and Hudack, S. S.: The Participation of Skin Lymphatics in Repair of the Lesions due to Incisions and Burns. Jour. Exper. Med., **60**, No. 4, 479–501, October 1, 1934.

5 Allen, H. S., and Koch, S. L.: The Treatment of Patients with Severe Burns. S. G. & O., **74**, 914–924, May, 1942.

6 Siler, V. E.: Primary Cleansing, Compression and Rest Treatment of Burns. S. G. & O., **75**, 161–164, August, 1942.

7 Owens, N.: Personal communication.

8 Rosenthal, S. M.: Experimental Chemotherapy of Burns and Shock. III. Effects of Systemic Therapy on Early Mortality. Public Health Reports, **58**, No. 13, 513–522, March 26, 1943.

DISCUSSION.—DR. SUMNER L. KOCH (Chicago, Ill.): Some years ago Evarts Graham wrote an admirable paper entitled "Principles *versus* Details in the Treatment of Empyema." One could well apply his identical words to this discussion of burns, for in no field of surgery is the emphasis on principles rather than details more important. The persistent search for some magic substance to apply to the burned area has served chiefly to befog our outlook in the problem of burn treatment and to divert our attention from the principles that Dr. Whipple has stressed so clearly and emphatically. I can only attempt to second his emphasis and repeat, in a little different way, what he has expressed so well.

Three simple principles cannot be overemphasized; they are concerned particularly with *prevention* of complications. The first principle—prevent infection, the most important *local* complication of a burn; the second, prevent loss of plasma, the most important *general* complication; the third, prevent contractures and long delay in healing—the important complications in deep burns, by replacing areas of whole-thickness loss as early as possible with skin grafts.

In spite of an increasing awareness of the importance of preventing infection of the large open wound, there is not yet widespread and general recognition of the fact that the important source of infection is the uncovered mouth and nose of first aid workers, nurses and surgeons who are caring for the patient. We have long been guilty of gross inconsistency in not giving the patient with an extensive open wound the protection that is deemed essential for the patient with a small wound cared for in the operating room.

How *can* we prevent infection? By covering the burned area immediately with clean towels and not exposing it even momentarily until personnel with masked faces and cleansed hands are ready to carry on. The practicability and helpful results of such protection were demonstrated by Churchill, and his associates, at the Massachusetts General Hospital after the Cocoanut Grove fire. Burned surfaces were covered with sterile towels in the emergency room, and kept covered until the patients could be cared for by masked, gowned and gloved personnel.

Aldrich's studies, Cruikshank's, and the observations of many other workers, show that infection of the burned surface takes place during the early period of treatment. It can be prevented in the majority of cases by recognition of the important potential

sources of infection, and by protecting the open wound from them. It may well prove that the addition of sulfathiazole in an oily base, as recommended by Dragstedt, and his associates, and by Gurd, and his coworkers, at the Montreal General Hospital, or of sulfanilamide, as recommended by Evans, can be of real value in preventing development of infection, but elimination of potential sources of infection is imperative.

How *can* we prevent fluid loss? By providing an absorbent compression dressing over the cleansed burn surface at the earliest possible moment. Such a dressing as Siler, Reid, and their associates, and, more recently, Neal Owens and Gurd, have demonstrated so effectively, checks the oozing from the burned surface and checks and limits the fluid loss into the subcutaneous tissues. Its value is nowhere more quickly recognized than in burns of the face and extremities, where the swelling and edema that develop so rapidly under a loosely applied or a coagulant dressing can be almost completely prevented by the application of a voluminous gauze dressing compressed with the aid of an inexpensive resilient material like mechanics waste and with an elastic bandage.

If fluid must be replaced, there is no argument as to the need and value of plasma, but here, just as with infection, there can be no question as to the value of the ounce of prevention as compared with the cost, the difficulty, and the time lost in providing the pound of cure.

Concerning the third principle—early replacement of areas of whole-thickness loss—one can only repeat that no chemicals, no ointments, and no witchcraft, that have yet been devised, can produce a covering of epithelium when the whole-thickness has been destroyed. Such a raw surface, as Blair, Brown and Byars, Padgett, McClure, and practically every surgeon who has faced the problem of caring for serious burns, have repeatedly emphasized, can be covered only by the slow growth of epithelium from the periphery or by transplantation of skin. The earlier such transplantation can be successfully accomplished the sooner will the patient be well and the less will be the scar tissue contracture that invariably results from long delay in healing.

In these three simple principles—prevention of infection; prevention of fluid loss; and prevention of long delay in healing by early grafting—"hang all the law and all the prophets." If we can state them so clearly that the surgical profession will recognize their force and be guided by them, we can well leave the less important details of treatment to the imagination and initiative of the individual surgeon.

Dr. Allen O. Whipple (New York City, closing): I should like to refer to one problem which has been touched upon, but just to show that there is a great deal of work being done on it. That is the problem of handling the third-degree areas after slough has been removed. There is a good deal of interesting work being done at the present time with enzymes that will hasten the removal of slough. Some of it appears to be promising.

Another factor which undoubtedly will facilitate the early grafting of these granulating surfaces is the proper concentration of sodium sulfadiazine, which in the ultramicroscopic form—that is, the centrifuged form—provides a film. I have seen some cases recently, in the Harlem Hospital, where the granulating surface has been frosted with this sulfadiazine, and grafts put on that area adhere very firmly and take amazingly well.

These cases are of particular interest to me because the grafts take apparently more easily, and the donor areas treated in the same way are available in an astonishingly short time for further skin grafts. I never have seen that done before, but I saw some areas where skin grafts had been removed ten days previously, that is epithelium from those same areas were removed to provide further grafts. This is a method which, in some of the very extensive burns, is a terrible problem, because you can not get large Paget grafts from these patients, and you have to use small areas of skin. It is just an example of how these patients which survive now, and which always died previously, are providing problems that we never had before.

GELATIN AS A PLASMA SUBSTITUTE: WITH PARTICULAR REFERENCE TO EXPERIMENTAL HEMORRHAGE AND BURN SHOCK*

W. M. Parkins, Ph.D., C. E. Koop, M.D., C. Riegel, Ph.D., H. M. Vars, Ph.D., and J. S. Lockwood, M.D.

Philadelphia, Pa.

FROM THE HARRISON DEPARTMENT OF SURGICAL RESEARCH, SCHOOLS OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA

Restoration and maintenance of circulating plasma volume are generally recognized as basic essentials in the prevention and treatment of shock. The successful use of crystallized human albumin indicates that the colloid osmotic pressure of plasma protein maintaining fluid distribution and plasma volume is a major physiologic factor in plasma and whole blood therapy.

In view of the difficulties of obtaining and preserving sufficient quantities of human plasma, it is natural to hope that the supply of plasma can be supplemented by a substitute which will be stable, innocuous, therapeutically effective, readily available, and reproducible with respect to its physiochemical properties. Many macromolecular colloids such as gum acacia, hemoglobin, bovine albumin, pectin, and a number of special gelatin preparations, including isinglass, have been, and are being, investigated. Hogan[1] reported, in 1915, that gelatin-saline infusions administered to patients in shock would restore falling blood pressure. Wolfson and Teller[2] found gelatin effective in experimental hemorrhage in the rabbit. Bayliss,[3] in 1917, and Rous and Wilson,[4] in 1918, strongly advocated the use of gum acacia, in preference to gelatin, in treatment of hemorrhage and shock. Although gum acacia has been used extensively, more recent study of its toxicity, especially with reference to its antigenicity, and its tendency to produce liver dysfunction and hypoproteinemia[5, 6, 7] has placed it in disfavor, except in emergency conditions when no other substitute is available.

Renewed interest in the possibilities of gelatin as a blood substitute is evidenced by a number of recent investigations (Taylor and Waters,[8] Waters,[9] Gordon, Hoge and Lawson,[10] Ivy, Greengard, Stein, Grodins and Dutton,[11] Little and Wells,[12] Ely and Angulo,[13] and Grodins.[14]

The aim of our study has been to determine: (1) The response of the

* The Charles B. Knox Gelatin Co. and Kind and Knox Gelatine Co., Johnstown, N. Y., and Camden, N. J., supplied the material, through the courtesy of Dr. D. Tourtellotte, and provided the University of Pennsylvania with a grant to defray a part of the cost of this study.

These studies were initiated by Drs. Norman E. Freeman and A. E. Schecter, who were forced to discontinue the work because of entering military service.

Preliminary reports of this work were presented at two conferences on gelatin, which were convened by the Subcommittee on Blood Substitutes of the National Research Council, in Washington, D. C., November 10, 1942, and February 23, 1943; and at the meeting of the Physiological Society of Philadelphia, April 20, 1943.

Read before the American Surgical Association, May 13–14, 1943, Cincinnati, Ohio.

normal dog to moderate and massive single and repeated infusions of bone collagen gelatin, with particular reference to general and specific toxic effects, many of which have been reported for other colloidal substances tested and used as blood substitutes; (2) the disappearance from the blood and excretion of gelatin; and (3) the efficacy of gelatin as compared with saline and plasma in the replacement of colloid osmotic pressure and plasma volume of dogs subjected to standardized conditions of hemorrhage or burn of a degree which is fatal to the untreated animal.

MATERIAL AND METHODS

The gelatin used in these studies was supplied as calcium gelatinate (Lot No. B78-1) produced by hydrolysis of alkali-treated bovine long-bone collagen, under controlled and standardized conditions. Our laboratory preparation was a six per cent solution in 0.85 per cent saline, sterilized by autoclave at 15 pounds pressure for 20 minutes. Aerobic and anaerobic sterility tests were uniformly negative. Although freshly prepared solutions were used routinely in these experiments, the preparation is stable for months when stored at 4°C. The solution after autoclaving has a p_H of 6; a specific viscosity of 1.6 at 37°C.; specific gravity of 1.024; and an osmotic pressure of 46 to 48 mm. Hg.

An 0.85 per cent saline solution was made from Sharp and Dohme sodium chloride tablets especially prepared for infusion purposes. The water was single-distilled and was neither tested nor treated for pyrogenicity. Fresh solutions were filtered and autoclaved at 15 pounds pressure for 20 minutes. Heparinized or citrated, pooled dog plasma was prepared from blood drawn under aseptic conditions from healthy animals.

All dogs used in these studies were carefully selected with regard to uniformity of nutritional state, age, size and general physical condition. They were acclimated to the laboratory and maintained under observation in individual cages for a period of at least one week prior to their use, and were fed a standard diet of Purina Checkers, with an occasional supplement of table or meat scraps.

Infusions were made by needle puncture through the jugular vein, and the apparatus was chemically clean and sterile. The solutions were kept at 32° to 37°C., and were administered at a rate of 0.5 to 1.0 cc. per kilogram per minute.

Blood pressure was determined in the femoral artery, by needle puncture, and mercury manometer and blood samples were withdrawn through the same needle.

Hematocrit determinations were made on heparinized blood in Wintrobe tubes, centrifuged at 2500 R.P.M. for 30 minutes. Plasma specific gravity determinations were made by the falling-drop method of Barbour and Hamilton.[15] Bromsulphalein retention was determined by the method of Rosenthal and White,[16] as modified by Helm and Machella.[17] Prothrombin time was measured by the procedure of Quick.[18] When plasma was analyzed

for plasma proteins and gelatin protein concentration, the differential precipitation of gelatin from plasma proteins was carried out with a modification of the method described by Waters.[16] The urine gelatin concentrations were determined by use of both tungstic and tannic acid preparation, and all nitrogen analyses were made with the aid of semimicro Kjeldahl apparatus.

EXPERIMENTAL STUDIES

I—INTRAVENOUS GELATIN IN NORMAL DOGS

1. *General Reactions.*—Following infusion of 30 and 60 cc. per kilogram of body weight (representing a 60 to 120 per cent increase in plasma colloid), all animals showed marked hemodilution, and with the larger doses, at least a temporary increase in blood pressure. The pulse and respiratory rates were increased for several hours after infusion. Nausea and emesis frequently occurred within two to three hours; and defecation occasionally followed within the same interval. Similar reactions often followed infusion of comparable volumes of saline or plasma. The animals usually appeared somewhat depressed and inactive for from three to six hours after the infusion of gelatin. By the following morning they were eager for food. Animals which received repeated infusions of gelatin, during a prolonged period, gained weight and remained in excellent general physical condition.

2. *Toxicity Studies*—(a) *Observations on Pyrogenicity.*—In 20 experiments upon ten normal dogs the temperatures were recorded at intervals of 15 minutes, 1, 2, 3, 4, 5, 6, and 24 hours after infusion of 30 cc. of gelatin per kilogram. At 15 minutes after infusion, the temperature was normal or somewhat below, with a slight increase by the second hour, reaching a peak between two and four hours, showing an average increase of 0.7° C. at three hours. The range was from no change to a maximum of 1.1° C. with a return to normal by the sixth hour. In four cases there was a slight temporary decrease in temperature. In four dogs infused with 10 cc. of gelatin per kilogram, no temperature rise was noted.

In four normal dogs subjected to massive hemorrhage (about 50 per cent of blood volume) followed by immediate infusion with an equal amount of gelatin, the temperature of one rose 1.0° C. in three hours, while that of two dogs dropped 1.1° C., and that of the fourth remained unchanged. Five dogs, bled in the same way (by needle puncture without anesthesia), and infused with sterile isotonic saline solution, showed a drop of 0.3° C. in one case, no change in two, and rise of 0.9° C. in the remaining two.

In view of the fact that the temperature changes with saline were similar to those with gelatin, when comparable volumes were administered, and considering the absence of temperature rises in the dogs receiving 10 cc. of glatin per kilogram, it appears doubtful that the gelatin *per se* is pyrogenic in the dog. Pyrogen tests in rabbits are in progress.

(b) *Observations on Antigenicity.*—Purified gelatin is generally considered to be nonantigenic.[19, 8, 9, 10] Sixteen normal dogs and five subjected to hemorrhage, were repeatedly infused with gelatin in amounts of 10 and

30 to 60 cc. per kilogram at intervals of days, weeks and months, without showing any evidence of anaphylaxis or sensitization as judged by blood pressure, respiration and other general reactions. Urticarial skin reactions commonly observed in dogs infused with dog plasma have in no instance been noted following infusion of gelatin. Animals have not yet been tested specifically for sensitization to other bovine protein.

(c) *Hematologic Observations:* Clotting Time, Pseudo-agglutination and Sedimentation Rate.—The clotting time of blood from dogs at various intervals after gelatin infusion (30 cc. per kilogram) was moderately increased. The average increase within 15 minutes was 16 per cent, and after three hours 30 per cent, with a return to normal within 24 hours. In two dogs subjected to triple hemorrhage and gelatin replacement, when a total of 90 cc. per kilogram was infused, the clotting time was about twice normal, and a return to normal occurred within 48 to 72 hours. Changes of the same order would be expected following infusion of similar volumes of citrated or heparinized plasma.

Pseudo-agglutination of erythrocytes has been reported to follow infusions of gelatin as well as other colloidal solutions used as blood substitutes.[20, 11, 14, 19] A pronounced increase in sedimentation rate after gelatin infusion was obvious to all who worked with the blood samples. Pseudo-agglutination and often massive clumping of erythrocytes were also apparent in the hematocrit blood samples, or when gelatin was mixed with red cells *in vitro*. However, the clumps which formed on standing were readily broken up with agitation.

Sedimentation rate determinations in gelatin-infused dogs, corrected for hematocrit changes, showed in most cases a two- to four-fold increase, with a return to normal as the gelatin disappeared from the blood stream. The increase in sedimentation rate was associated with, and apparently largely due to, the pseudo-agglutination of erythrocytes which occurred *in vivo* as well as *in vitro*. Direct observations and photomicrographs of this phenomenon *in vivo* were made by Dr. R. G. Abell, of the Department of Anatomy, using the ear-window technic in the normal unanesthetized rabbit. While the pseudo-agglutination of the red cells was present it did not appear to retard the circulation through the capillaries of the ear of normal rabbits infused with 15 cc. of gelatin per kilogram. The influence of this effect of gelatin, an effect which follows the administration of certain other colloids, upon the oxygenation of the blood and the peripheral circulation of animals in shock is deserving of further study, using special gelatin preparations.

(d) *Liver and Kidney Function.*—Observations on bromsulphalein retention, glucose tolerance, and prothrombin time, were undertaken as tests of liver function. Urea clearance was used as an index of kidney function.

Determinations were made before, and at intervals after, repeated weekly infusions of gelatin in 14 dogs. Three hours after each infusion of gelatin (30 cc. per kilogram) a marked retention of bromsulphalein was observed, which had diminished at 24 hours, and was essentially normal at 48 hours.

As illustrated in Figure 1, the degree of retention became increased, and the return to normal was increasingly delayed with each additional weekly infusion. The two dogs which showed the highest retention of bromsulphalein were selected for the illustration.

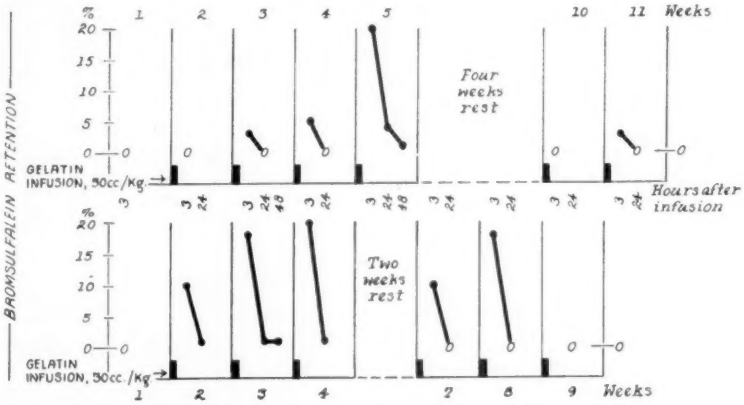


FIG. 1.—Bromsulfalein retention after weekly infusions of gelatin.

In animals in which the weekly infusions were suspended for a period of four or more weeks the retention of bromsulphalein after a subsequent infusion of gelatin was similar both in degree and duration to that following the first infusion of the series. However, the cumulative increase of bromsulphalein retention was present upon infusion following a rest of three weeks or less. It did not develop in dogs receiving weekly infusions of 10 cc. per kilogram.

Bromsulphalein retention was also determined after infusion of 30 cc. per kilogram of pooled heparinized dog plasma. Three of five dogs showed a bromsulphalein retention of as much as 16 per cent at three hours after a single plasma infusion.

The results of determinations of glucose tolerance after gelatin were variable, but no definitely abnormal curves were obtained.

The prothrombin time studies revealed normal values throughout except in one dog, which exhibited a prolonged time on two occasions as shown in Table I.

TABLE I

PROTHROMBIN TIME IN SECONDS

(Normal—under 21 seconds)

Weeks	208	243	273	296	300	
	9	17	13	9	13	Before first infusion
2	17			17	13	Between
3	14		13	14	14	3 and 4
4	(58)		12	11	11	hours
5		14				after
6	17	13		14		weekly infusions
7	(25)	14		16		of
8		13		16		gelatin
9					14	3% of body weight
10					16	
11		16				

The explanation of the bromsulphalein retention which follows massive gelatin and plasma infusions in normal unanesthetized dogs is not clear. In view of the transient nature of the retention after gelatin and plasma, it seems permissible to conclude that the liver dysfunction suggested by retention of bromsulphalein is probably not specific to gelatin itself and presents no serious obstacle to further clinical investigation of gelatin as a plasma substitute. It should be recognized that with an infusion of 30 cc. of gelatin per kilogram, the animal's plasma colloid would rise to about 160 per cent of normal unless temporary storage of gelatin or plasma protein occurred. It is during the period when a new colloid equilibrium is being reached that pseudo-agglutination of erythrocytes and retention of bromsulphalein are found. The repeated administration of smaller quantities of gelatin did not lead to cumulative retention of the dye.

(e) *Histologic Observations.*—With the collaboration of Dr. H. L. Ratcliffe of the Department of Pathology, there is in progress a thorough study of tissues from normal dogs and dogs subjected to hemorrhage, and from animals which succumbed to burn shock or were sacrificed at various intervals after infusions of gelatin, saline or plasma. A detailed report will be made upon completion of the observations. For the present, it can be stated that no evidence of chronic liver damage with storage of gelatin in the liver or other organs has been noted in normal dogs following single and repeated massive doses of gelatin. Tissue changes in liver, kidneys, and adrenals were only slightly more marked with gelatin than with plasma, and were definitely reversible.

II—DISAPPEARANCE FROM BLOOD, AND EXCRETION OF GELATIN

In a review of the literature on blood substitutes by Amberson,[19] it is concluded from publications on the use of gelatin preparations available 20 to 30 years ago that gelatin is relatively valueless because of the rapidity with which it leaves the blood stream. Waters[9] found calf skin gelatin to remain in the blood of infused animals much longer than does isinglass. Little and Wells[12] have recently shown that bone gelatin escapes through injured capillaries of the intestine more slowly than do the plasma proteins.

The basis of our interest in the rate of disappearance and the excretion of bone gelatin infused in normal dogs and in replacement of blood removed by a rapid massive hemorrhage was: (1) To correlate blood concentrations with other studies of efficacy and reactions to gelatin; (2) to determine whether the plasma proteins depleted by hemorrhage would be replaced in gelatin-infused animals at a rate sufficient to maintain total protein concentration, colloid osmotic pressure, plasma volume and blood pressure as the gelatin concentration decreased in the blood; and (3) to correlate the disappearance of gelatin from the blood with gelatin excretion, and with plasma protein concentrations, in the attempt to obtain information relative to the fate of gelatin and the question of its utilization as available protein.

Results.—Experiments on five normal dogs infused with 30 cc. of gelatin

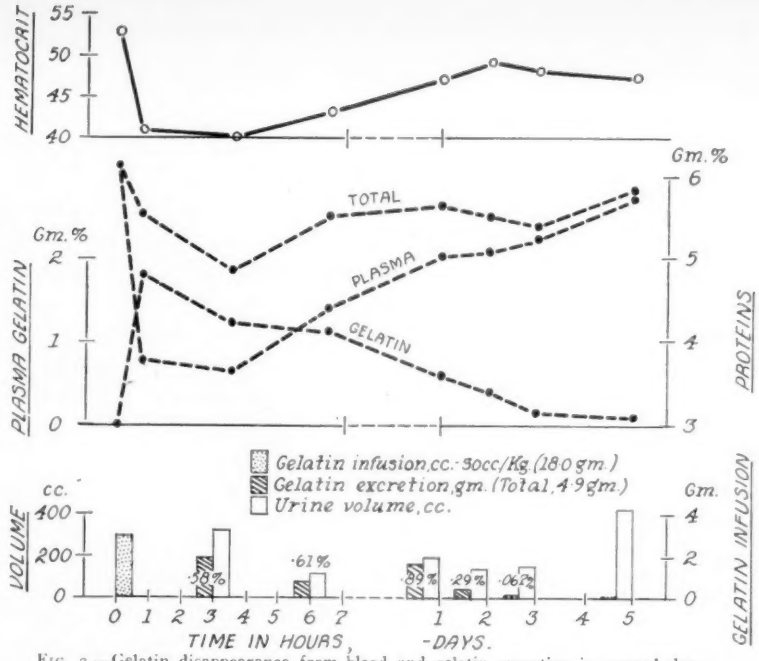


FIG. 2.—Gelatin disappearance from blood and gelatin excretion in normal dog.

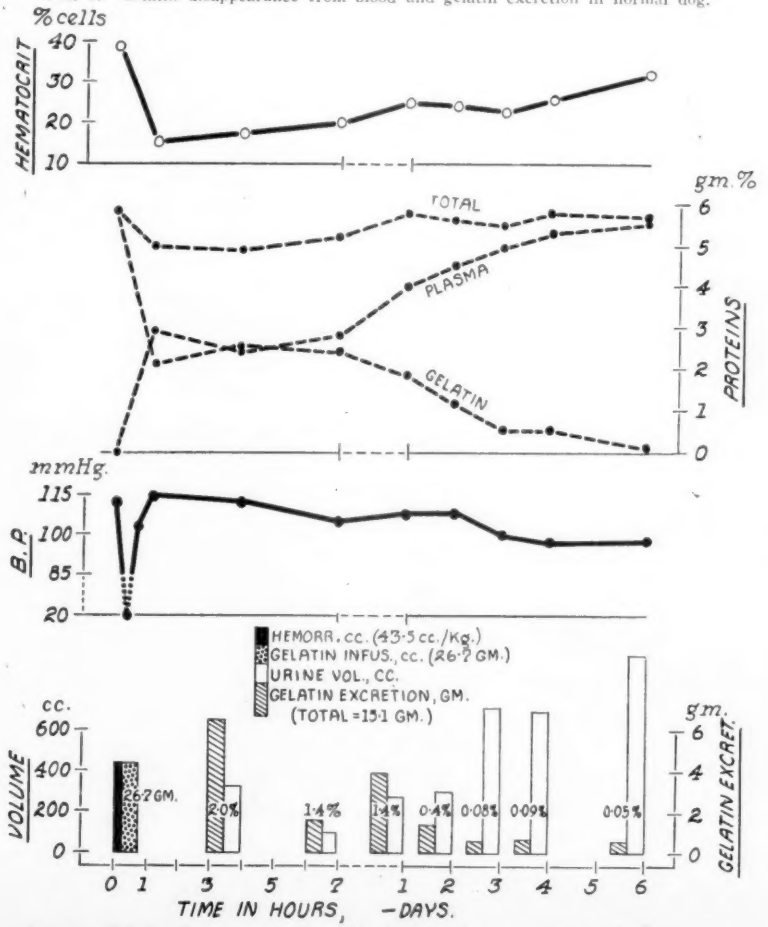


FIG. 3.—Gelatin disappearance from blood and gelatin excretion. Single massive hemorrhage.

per kilogram and on five unanesthetized dogs subjected to massive hemorrhage and infusion with a volume of gelatin equivalent to the volume of blood removed, are illustrated by representative data in Figures 2 and 3. It will be observed that a diuresis and relatively rapid excretion of gelatin occurred which decreased at six hours following infusion. Hemodilution and increased plasma volume, as indicated by hematocrit and plasma protein concentration, were well maintained in both the normal and the bled dogs, as was also the blood pressure following massive hemorrhage.

The plasma proteins were apparently replaced at about the same rate as that at which the gelatin disappeared from the blood stream. Following a brief period of osmotic adjustment to the high osmotic pressure of the infused gelatin, the total protein levels were well maintained in the experiments involving hemorrhage.

The decrease in total plasma protein concentration (including gelatin), which occurred soon after gelatin infusion, may be explained by increase in plasma colloid osmotic pressure and compensatory hemodilution, since the six per cent gelatin used has a colloid osmotic pressure about twice that of plasma. Determinations of plasma colloid osmotic pressure of blood drawn 15 minutes after gelatin replacement following hemorrhage, showed an increase of approximately 20 per cent.* Calculations indicate that the plasma volume is increased to an extent greater than the volume of fluid infused, which is in keeping with the increased osmotic pressure and consequent hemodilution from interstitial fluid.

Approximately one-half, or less, of the gelatin which leaves the blood stream is accounted for by the kidney excretion figures. The normal dog, in Figure 2, excreted 27 per cent of the gelatin infused; the dog subjected to hemorrhage (Figure 3), receiving a large amount, excreted 56 per cent. One other normal dog excreted 59 per cent.

Discussion.—The fate of gelatin which is not excreted remains obscure. Normal animals which received repeated weekly infusions of 30 cc. of gelatin solution per kilogram showed no indication of a deposition. Parenterally administered gelatin may be partially utilized in metabolism of the body tissues, or it may enter into maintenance or replacement of plasma proteins. That parenteral gelatin is metabolized to maintain nitrogen balance or equilibrium is indicated by the work of Brunschwig, Scott, Corbin and Moe.[21] Experiments now in progress will yield additional data relative to the question of the utilization of intravenously administered gelatin.

III—STUDIES ON HEMORRHAGE

COMPARISON OF GELATIN WITH SALINE AND PLASMA

Hemorrhage, by widely different procedures, and under various conditions, is commonly employed as a method by which the efficacy of potential blood substitutes may be evaluated. Unfortunately, there is no standard

* We wish to thank Doctors Tourtellotte and Williams, of the Kind-Knox Research Laboratories, for the colloid osmotic pressure determinations.

generally accepted procedure for this purpose. This fact makes difficult the comparison of results from different laboratories where various substitutes are under study.

Three bleeding procedures similar to those used experimentally by others, each of which is frequently parallelled in military or civilian injuries were employed in the following experiments. The efficacy of gelatin was compared under uniform conditions with saline or with saline and plasma. Conditions were such that few, if any, of the animals so treated would have survived without administration of one of the three infusion fluids.

I—SINGLE MASSIVE HEMORRHAGE AND IMMEDIATE INFUSION

Ten dogs were bled by arterial needle puncture, over a 10- to 15-minute interval, to the point of air hunger or respiratory failure, with the blood pressure falling to 15 to 20 mm. of Hg. Infusion was begun within two minutes. The volume infused was, in each case, equal to the volume of blood withdrawn. Four dogs, two in each infusion group, were given artificial respiration until the beginning of the infusion. Five animals were infused with gelatin, five were infused with saline.

Results.—The data are shown as average values in Table II. All these unanesthetized dogs survived the removal and replacement of approximately one-half of their total calculated blood volume. Obviously, survival as a

TABLE II

SUMMARY OF AVERAGE VALUES—SINGLE RAPID MASSIVE HEMORRHAGE
Immediate Infusion — Saline and Gelatin

Determination	Initial	Infusion	After Infusion					
			15 minutes		3 hours		24 hours	
				% Initial		% Initial		% Initial
Blood Pressure....	135	Gelatin	125	92.5	101	74.8	113	83.6
mm. Hg.....	134	Saline	90	67.0	105	78.4	118	88.0
Hematocrit.....	46	Gelatin	15	32.6	16	34.8	23	50.0
% cells.....	44	Saline	27	61.4	27	61.4	25	56.0
Total Protein	5.83	Gelatin	5.10	87.5	4.62	79.3	5.07	87.0
gm. %.....	5.22	Saline	3.21	61.5	3.74	71.5	4.28	82.0

criterion is of little value in determining the relative merits of infusion fluids under the seemingly severe conditions of hemorrhage in these experiments. A higher total protein concentration, a considerably greater decrease in hematocrit, and the return of blood pressure to normal within 15 minutes after gelatin infusion indicated a definite superiority of gelatin over saline in experimental hemorrhage of this type. Results from one such experiment in which gelatin disappearance and excretion were studied are illustrated by Figure 3.

DISCUSSION.—There is no general agreement in the literature regarding the efficacy of saline infusions in experimental hemorrhage.[22, 23, 24, 25, 26, 10, 11] It should be pointed out that animals show a remarkable spontaneous physio-

logic compensation to a massive rapid hemorrhage, if the brief critical period after hemorrhage is overcome by administration of any isotonic fluid. Even though the concentrations of plasma protein may be reduced, and the effect of saline in restoration of blood volume and pressure in some conditions may be transient, the administration of saline as a temporary expedient should not be ignored.

Conclusions as to therapeutic efficacy of a number of proposed blood substitutes have been based upon survival alone, or upon blood pressure elevation following infusion of a blood substitute in animals subjected to single rapid hemorrhage.[11, 8, 27] In those instances where the effect of saline alone was not determined under conditions of severe and otherwise fatal hemorrhage, the question may be seriously raised as to how much of the apparent influence of the blood substitute was a result of the fluid in which it was dissolved.

Under the conditions of single massive rapid hemorrhage and immediate infusion used in experiments illustrated in Table I, all of the dogs showed a definite hemodilution, increased blood pressure, and survived when saline or gelatin was infused. The early response to gelatin suggested its superiority over saline alone. However, the physiologic mechanisms of compensation were sufficient to make both groups more nearly comparable at three and 24 hours.

2—TRIPLE HEMORRHAGE AND INFUSION

A controlled triple hemorrhage procedure provided a more critical method of evaluating gelatin.

Dogs under nembutal anesthesia (25 mg. per Kg., intravenously) were bled 30 cc. per kilogram (approximately one-third their blood volume), and infused with an equal volume of gelatin, or saline. One hour after the first hemorrhage the animals were bled another 30 cc. per kilogram, or until the blood pressure dropped to 30 mm. of Hg. They were then infused. One hour later they were similarly bled and infused for the third time.

Results.—When saline was infused (Figure 4) the blood pressure returned to nearly normal levels after the first infusion, but was not well maintained and usually dropped to 30 mm. Hg. upon completion of the second hemorrhage. After the second infusion the blood pressure rarely returned to normal, and rapidly dropped to about 30 mm. of Hg. during the third hemorrhage. Only eight to 21 cc. per kilogram, with an average of 15 cc. per kilogram, could be withdrawn safely at the third bleeding, since a blood pressure below 30 mm. Hg. may be rapidly fatal. During the third infusion, the blood pressure rose to about 80 mm. of Hg. but was not sustained, even though additional saline may have been infused. However, two of the five dogs infused with saline recovered, even though the blood pressure remained at about 60 mm. Hg. for many hours. The plasma protein concentration was reduced to three to four Gm. per cent. The hemodilution

and increased plasma volume, as indicated by hematocrit and hemoglobin were well maintained.

The gelatin-infused dogs (Figure 5) were decidedly more resistant to this repeated bleeding. The blood pressure dropped but little more during the second hemorrhage than during the first; and in every case, the full

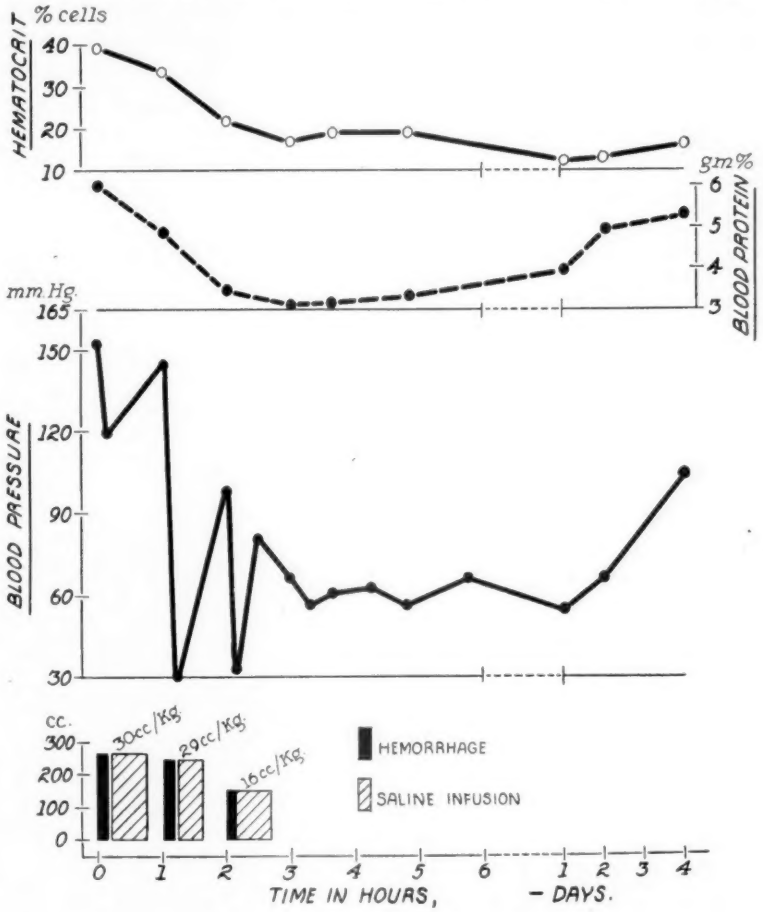


FIG. 4.—Saline in triple hemorrhage.

30 cc. per kilogram could be removed during the third hemorrhage without a decrease in blood pressure to critical levels. Three such dogs maintained a nearly normal blood pressure after the third infusion of gelatin, and recovered. With gelatin infusion the total protein levels were well maintained, and hemodilution was marked.

Two additional dogs were bled to a total of 100 cc. per kilogram, in three hemorrhages, followed by immediate infusions with gelatin. These two animals succumbed within 16 hours, even though the blood pressure fell to only 46 and 68 mm. of Hg., respectively, upon the third bleeding, and rose again to 74 and 80 after the third replacement with gelatin. Hematocrits

were 6.6 to 8.0 per cent, respectively, and the animals were markedly dyspneic. No erythrocytes were replaced in any of the triple hemorrhage experiments. It appears probable that death of these two dogs was due largely to anoxemia, resulting from a too drastic reduction in numbers of erythrocytes, rather than to depletion of plasma volume. The contrast between the gelatin and the saline-infused animals was most striking in the response to a third hemorrhage. Only eight to 21 cc. per kilogram, with an average of 15 cc., were bled from the saline-infused animals to reduce blood pressure to 30 mm.

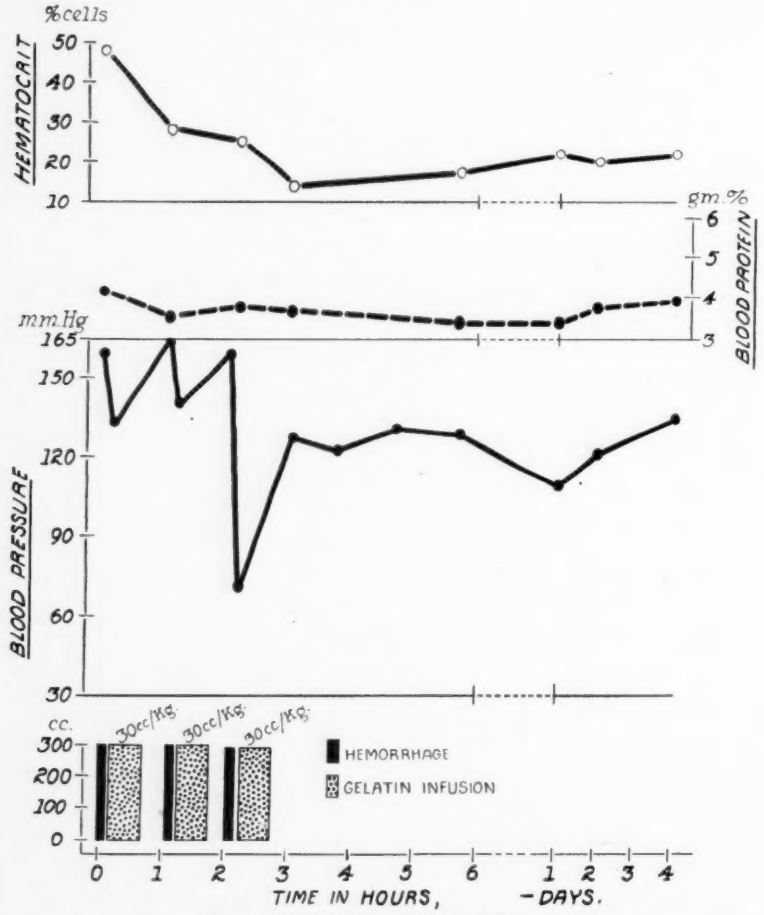


FIG. 5.—Gelatin in triple hemorrhage.

Hg. Thirty cubic centimeters per kilogram could be withdrawn during the third hemorrhage from each of the animals infused with gelatin, without reducing blood pressure to such a critical level.

The dog illustrated in Figure 6 showed definite and maintained improvement following gelatin infusions, although prior saline infusions had failed to restore stability of the blood pressure. Total protein concentration, hemodilution and blood pressure were increased and well maintained after

each gelatin infusion. Despite a blood pressure of 50 mm. of Hg., and below, for several hours during the period of saline infusion, the administration of gelatin was followed by complete recovery.

3—PROLONGED HEMORRHAGE AND SUSTAINED HYPOTENSION

The spontaneous compensation of the dog to hemorrhage, and the effectiveness of fluid replacement are markedly influenced by the rate of bleeding, and the degree and duration of the hypotension.[28, 29, 30, 31, 32] When the bleeding was prolonged or intermittent, and the blood pressure main-

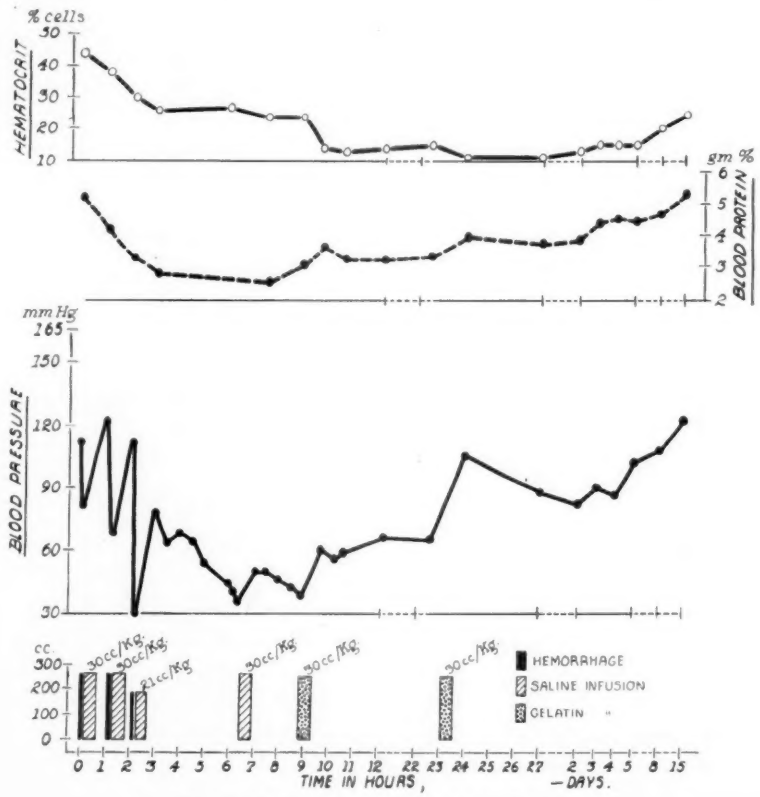


FIG. 6.—Saline-gelatin in triple hemorrhage.

tained at critically low levels by subsequent repeated withdrawals of blood, the response to a replacement of plasma volume is altered and the adequacy of the infusion fluid correspondingly diminished. Although hemodilution and increase in plasma volume and blood pressure occur after infusion of fluids, determining factors apart from blood volume in the blood pressure maintenance, such as peripheral resistance, may not be adequately compensated for by the infusion, and the circulation may fail.[30, 33]

In the following experiments gelatin as a plasma substitute was studied by comparison with saline and also with plasma under conditions wherein

saline was of little value in the majority of cases, and plasma was uniformly effective.

Sixteen dogs, under nembutal anesthesia, were bled in three stages, over a period of 30 to 40 minutes. Mean arterial blood pressure was maintained between 30 and 40 mm. Hg. for 30 to 40 minutes by additional bleeding if the blood pressure rose above 40. If the blood pressure dropped two

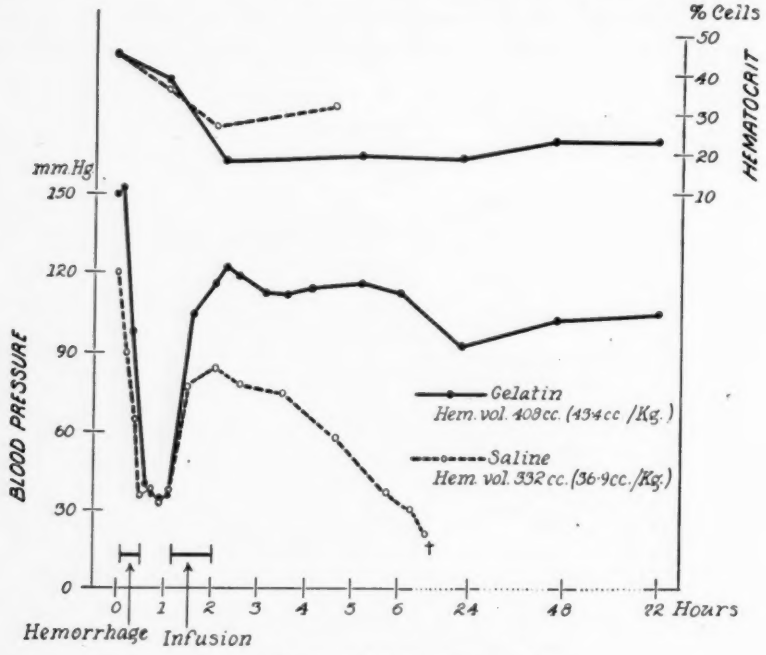


FIG. 7.—Gelatin and saline in hemorrhage.

or three millimeters below 30 mm. Hg. whole blood was injected in order to maintain the pressure at approximately 35. An infusion volume of the substitute equal to the volume of blood withdrawn (minus the amount replaced in keeping the animal alive during the hypotensive period) was administered at a uniform rate in each case.

Results.—Three untreated dogs succumbed within two and one-half hours. Three of five saline-infused dogs died within two to six hours; although the blood pressure after infusion was poorly maintained, two dogs recovered in spite of persistently low blood pressures of between 60 and 80 mm. Hg. for many hours after infusion. The blood pressure of all five gelatin-infused animals was increased to over 100 mm. Hg. upon injection of approximately 50 per cent of the infusion volume; it was further increased and well maintained following completion of the infusion (Figure 7). Complete recovery was rapid and uneventful in all five animals.

Three dogs infused with plasma reacted in much the same manner as did the gelatin-infused dogs, and all recovered. Figure 8 is typical of all

plasma and gelatin-treated animals. The hemodilution and increase in plasma volume, as indicated by hemoglobin and hematocrit, was more marked after gelatin infusion than after plasma. This may be due to the fact that the six per cent gelatin preparation used has a colloid osmotic pressure value

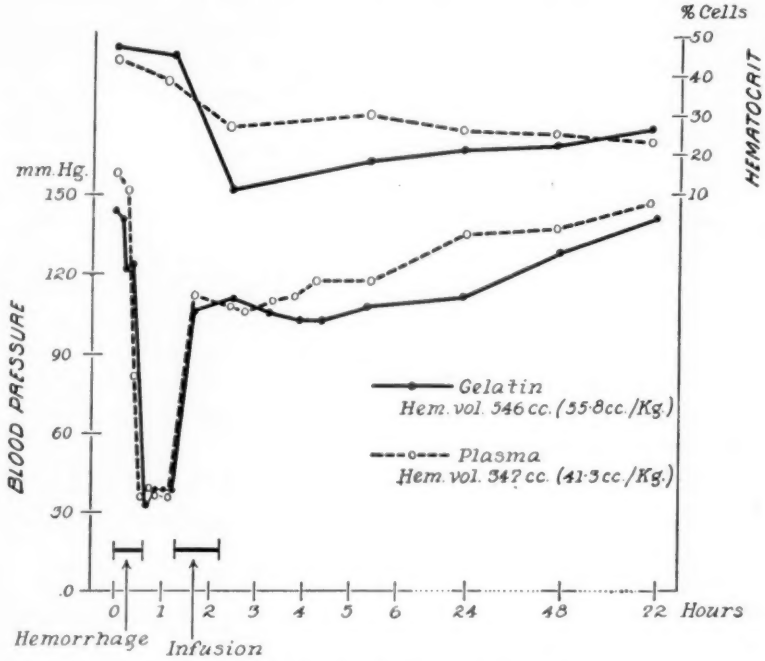


FIG. 8.—Gelatin and plasma in hemorrhage.

greater than that of plasma. Gelatin, under the conditions of this experiment, is undoubtedly superior to saline, and compares favorably with plasma as an effective blood substitute in maintenance of colloid ismotic pressure, blood volume and blood pressure. Gelatin thereby permits complete recovery of animals from a state of posthemorrhagic hypotension, which is fatal to untreated controls and to a majority of saline-infused animals.

DISCUSSION.—The question may be asked how gelatin compares with plasma and other plasma substitutes in experimental hemorrhage, under more drastic conditions where even plasma is not uniformly adequate for survival. Experiments now in progress, involving further prolongation of the period of hypotension, tend to indicate that under such extreme conditions the gelatin solution as now constituted falls short of being a complete replacement for plasma. Although the increase in blood volume may be even greater, and may be as well maintained after gelatin as after plasma, the blood pressure is more adequately sustained and survival more definitely assured with plasma than with gelatin. Hemodynamic factors, in addition to replacement of colloid osmotic pressure and plasma volume, enter into a consideration of complete recovery in these experiments.

In general, the results from a rather small number of dogs subjected to experiments on hemorrhage have led us to the tentative conclusion, that gelatin because of its colloid osmotic properties is definitely superior to saline, but may be deficient in some of the beneficial properties of whole blood or plasma. When tested under conditions where replacement of colloid osmotic pressure and plasma volume are sufficient, that is, before the exhibition of the so-called "irreversible" factors described by Wiggers[30, 33, 34] gelatin compares favorably with plasma.

IV—GELATIN IN BURN SHOCK

Although a given blood substitute may be found to be entirely satisfactory in the treatment of hemorrhage or posthemorrhagic shock it may or may not be equally efficacious in treatment of other shock states, such as those following thermal or mechanical injuries. Ely and Angelo[13] have concluded from their observations on rabbits subjected to sublethal burns, that a gelatin-glucose-salt solution is as effective as plasma in combatting the hemoconcentration. Grodins[14] recently reported that gelatin-saline is much more effective than saline alone, and about equal to plasma, in producing a sustained rise in blood pressure of dogs in shock resulting from limb trauma.

In studies of gelatin as a plasma substitute in burns, it seemed important to determine the hemodilution, blood pressure and other criteria of colloid osmotic pressure and fluid distribution in the first 12 to 24 hours, and also the later response of the treated animals in the so-called "acute toxemia" phase.

Eight of 30 dogs burned were used in trials to determine, by a controlled reproducible procedure (similar to that described by Trusler, Egbert and Williams[35]), the degree of injury which would be fatal to most if not all untreated animals; a burn not so severe as to be irreversible, but one in which plasma therapy might still be effective. The following procedure was used in the 22 dogs included in this report: The hair of the animal was closely clipped from the hindquarters and body, up to the axillae. The animal was anesthetized with morphine and amytal, then immersed up to the axillae in water at 72° C. for 60 seconds. Ether was used to supplement the anesthesia during the immersion. Observations were continued to death, or for a period of 72 to 96 hours of survival, at which time the recovering animals were sacrificed for pathologic study. All dogs were infused with 30 cc. per kilogram of body weight of the test solutions, at comparable intervals of time (two and nine hours) following the injury. The volume of the third infusion varied between 1.5 per cent and 3.0 per cent of body weight, depending upon the extent of the hemoconcentration at the time. Other conditions were kept uniform, including the taking of blood samples and blood pressure determinations. The animals were permitted to recover from the anesthesia. Sulfathiazole ointment was used to control skin infections.

Results.—The average survival time of five untreated animals was 11 hours, with a range of from four to 19 hours. Of the five saline-treated animals, two recovered, and were sacrificed at 72 hours, while three succumbed within nine to 20 hours, with an average survival of 13 hours. One gelatin-infused dog recovered; seven died in from nine to 67 hours, with an average survival of 28 hours. Three of the four plasma-treated dogs recovered; one of the plasma animals died at nine hours, just previous to the second infusion.

Although the hemodilution effect of saline was slight in comparison with gelatin or plasma, it appeared that saline alone was beneficial to these animals. Two dogs survived the first 12- to 24-hour period of critical plasma leakage, reached the stage when compensatory blood volume control was reestablished, and hemoconcentration spontaneously disappeared while the blood pressure was maintained.

The rapid progressive hemoconcentration, due essentially to leakage of plasma into the injured area through capillaries permeable to protein, was well compensated by gelatin infusions. Figure 9 is representative of typical cases in each of the four groups of animals. The colloid osmotic pressure of the plasma protein appeared to be adequately replaced by gelatin, since the hematocrit and hemoglobin levels could be brought to normal, and were about as well maintained as with the infusion of equivalent volumes of plasma, as shown by Figure 9 and Table III. The rate of hemoconcentration following the first and second infusions of gelatin, as compared with that following plasma infusion, suggests that the gelatin molecules may be as well retained by permeable capillaries as are the plasma proteins.

Discussion.—With gelatin infusions the survival of the animals could be extended beyond the period when plasma loss into the burned area might be considered to be a cardinal factor. Although the hemoconcentration was corrected, the blood pressure was not permanently maintained and, with the

Table III

SUMMARY OF AVERAGE VALUES
HEMOCONCENTRATION (HEMATOCRIT) OF DOGS SEVERELY BURNED

Treatment	No. of Dogs	Hematocrit (% cells) Normal	Per Cent of Normal			
			Infusion I		Infusion II	
			Before	After	Before	After
Saline	5	44	136	126	153	127
Gelatin	8	42	137	105	145	95
Plasma	4	45	140	116	149	94

exception of one dog, the animals, nevertheless, succumbed. The mechanism involved in this circulatory collapse which is unassociated with hemoconcentration in the secondary phase of burn shock remains obscure. The possibility of functional impairment of some vital organ such as liver, adrenal or kidney,

already damaged through anoxia or through absorption of some hypothetic toxic substance from the burned area, has not been excluded.

Since gelatin compensates for the osmotic pressure of lost plasma protein and apparently corrects the plasma volume deficiency of burn shock, we are determining whether or not the efficacy of gelatin in burn treatment may be enhanced through modification of the gelatin solution or its technic of administration, and through the concomitant use of accessory humoral factors.

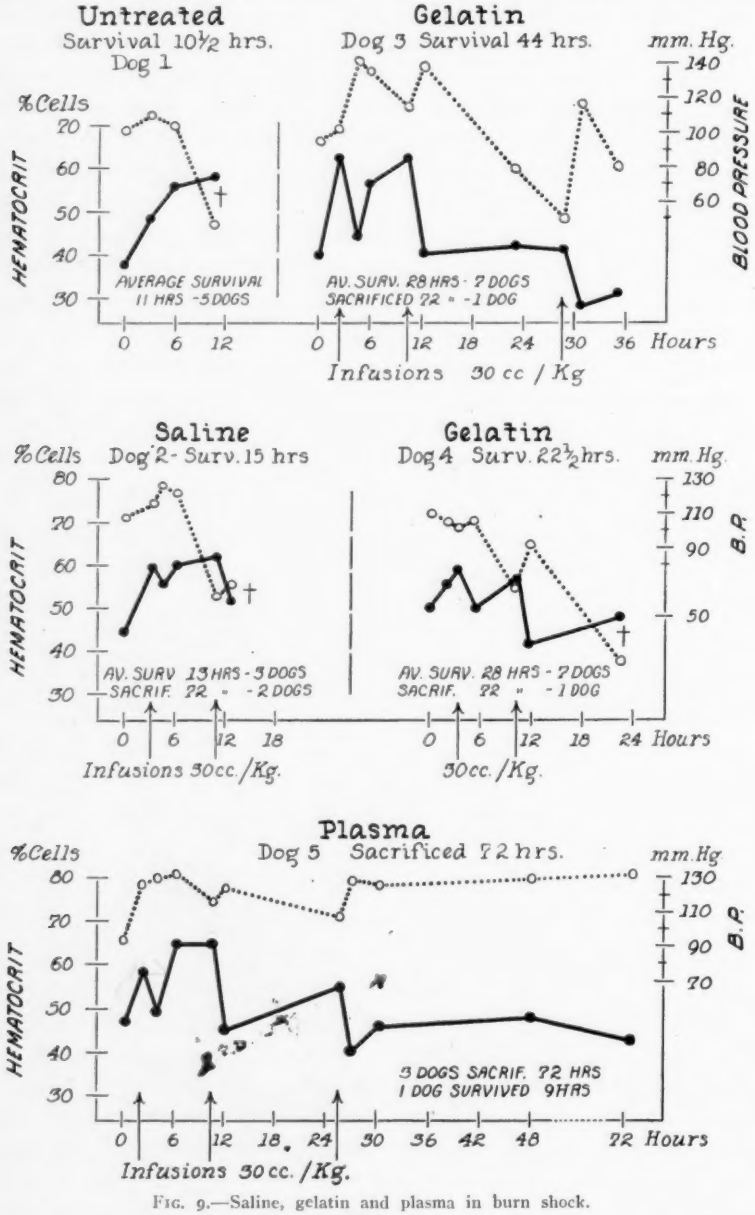


FIG. 9.—Saline, gelatin and plasma in burn shock.

SUMMARY AND CONCLUSIONS

1. Normal dogs tolerate repeated infusions of large volumes of gelatin-saline solution without any serious toxic reactions specific to gelatin. Unfavorable reactions that do occur are reversible and are frequently produced by infusions of comparable amounts of saline or plasma.

2. Pseudo-agglutination of erythrocytes and increase in sedimentation rate, which also occur following infusion of other macromolecular colloids, have been observed both *in vitro* and *in vivo* following infusions of gelatin.

3. Bromsulphalein retention occurred after repeated infusions of gelatin but is present to some extent, in dogs infused with comparable volumes of plasma. Other liver function tests were essentially negative.

4. Kidney function, as determined by urea clearance, was apparently unimpaired after single and repeated infusions of gelatin in normal dogs.

5. Tissue changes observed histologically were reversible and slightly more marked with gelatin than with plasma infused in equivalent volumes and under similar conditions. No chronic tissue storage was observed in animals which received repeated infusions of large volumes of gelatin.

6. A transient diuresis and excretion of gelatin followed its infusion in normal dogs and dogs subjected to preliminary hemorrhage. About half of the gelatin infused was accounted for by urinary excretion.

7. Following massive, rapid hemorrhage and immediate infusion of gelatin, the plasma proteins were apparently replaced at about the same rate as that at which the gelatin protein disappeared from the blood stream.

8. All dogs survived a rapid, massive hemorrhage to point of respiratory failure and blood pressure levels of approximately 20 mm. Hg. when immediately infused with either saline or gelatin. The higher total protein concentration following gelatin infusion, the considerably greater hemodilution, and the more rapid return of the blood pressure to normal, strongly bear out the superiority of gelatin over saline in experimental hemorrhage of this type.

9. The resistance of the dog to repeated massive hemorrhage, followed by gelatin infusion is markedly increased over that of the animal similarly bled and infused with saline. The saline-infused dog in which the blood pressure continued to decline and remained at critical levels for hours following repeated infusions completely recovered upon subsequent infusions of gelatin.

10. Following a slow, three-stage hemorrhage, with blood pressure maintained at 30 to 40 mm. Hg. for 30 to 40 minutes, all untreated dogs succumbed within a few hours. Although elevation of plasma volume and blood pressure were not marked or well maintained after infusion of saline, compensation occurred and two of five dogs slowly recovered. Three of the saline-treated animals died in two to six hours. Gelatin infusion resulted in a more marked hemodilution than did plasma infusion under uniform volume replacement. The blood pressure was restored and main-

tained at approximately the same normal levels with gelatin as with plasma, and all dogs made a rapid, complete recovery under these conditions of experimental hemorrhage, gelatin appears to be a suitable substitute for plasma.

11. In eight dogs subjected to a standardized, reproducible burn of a degree fatal to untreated animals and to a majority of saline-infused animals, gelatin solutions compensated for the loss of plasma from the blood stream, and corrected hemoconcentration to the same degree as did plasma infused in four animals. Although survival was extended in the burn shock gelatin group beyond the period when death occurred in controls, presumably from hemoconcentration, seven of eight dogs succumbed after progressive decline in the blood pressure, unassociated with hemoconcentration. Under identical conditions, with plasma infusion, only one of four dogs succumbed.

12. If a factor can be identified in plasma which accounts for its ability to maintain blood pressure in the severely burned animal during the secondary phase of so-called "acute toxemia," the addition of this factor to gelatin would probably result in a more adequate plasma substitute for burns.

REFERENCES

1 Hogan, J. J.: The Intravenous Use of Colloidal (Gelatin) Solutions in Shock. J. A. M. A., **64,** 721, 1915.

2 Wolfson, W. L., and Teller, F.: The Intravenous Use of Gelatin Solution in Hemorrhage. Am. J. Med. Sci., **178,** 562, 1929.

3 Bayliss, W. M.: Methods of Raising a Low Arterial Pressure. Proc. Roy. Soc. London, Ser. B, **89,** 380, 1917.

4 Rous, P., and Wilson, G. W.: Fluid Substitutes for Transfusion after Hemorrhage. J. Am. Med. Assoc., **70,** 219, 1918.

5 Maytum, C. K., and Magath, T. B.: Sensitivity to Acacia. J. A. M. A., **99,** 2251, 1932.

6 Andersch, M., and Gibson, R. B.: Studies on the Effects of Intravenous Injections of Colloids. I. Deposition of Acacia in the Liver and Other Organs and its Excretion in Urine and Bile. J. Pharm. and Exper. Therap., **52,** 390, 1934.

7 Yuile, C. L., and Knutti, R. E.: Blood Plasma Proteins as Influenced by Intravenous Injection of Gum Acacia; S. Production of Chronic Hypoproteinemia. J. Exper. Med., **70,** 605, 1939.

8 Taylor, N. B., and Water, E. T. Isinglass as a Transfusion Fluid in Hemorrhage. Canad. Med. Assoc. J., **44,** 547, 1941.

9 Waters, E. T.: A Comparison of Isinglass and Gelatin as Blood Substitute. Canad. Med. Assoc. J., **45,** 395, 1941.

10 Gordon, H., Hoge, L. J., and Lawson, H.: Gelatin as a Substitute for Blood After Experimental Hemorrhage. Am. J. Med. Sci., **204,** 4, 1942.

11 Ivy, A. C., Greengard, H., Stein, I. F., Jr., Grodins, F. S., and Dutton, D. F.: The Effect of Various Blood Substitutes in Resuscitation After an Otherwise Fatal Hemorrhage. Surg., Gynec. and Obst., **76,** 85, 1943.

12 Little, J. M., and Wells, H. S.: Capillary Permeability to Intravenously Administered Gelatine. Am. J. Physiol., **138,** 495, 1943.

13 Ely, J. O., and Angulo, A. W.: Experimental Burns: The Influence of a Gelatin-Glucose-Salt Solution on the Hemoconcentration of Burns. J. of the Franklin Instit., **235,** 197, 1943.

14 Grodins, F. S.: Gelatin as a Blood Substitute in Shock due to Limb Trauma. Federation Proceedings, **2**, 17, 1943.

15 Barbour, H. G., and Hamilton, W. F.: The Falling-Drop Method for Determining Specific Gravity. J. Biol. Chem., **69**, 625, 1926.

16 Rosenthal, S. M., and White, E. C.: Clinical Application of the Bromsulphalein Test for Hepatic Function. J. A. M. A., **84**, 1112, 1925.

17 Helm, J. D., and Machella, T. E.: Significance of Dosage and Time Factors on the Value of the Bromsulphalein Test for Liver Function. Am. J. Digest. Dis., **9**, 141, 1942.

18 Quick, A. J.: The Clinical Application of Hippuric Acid and Prothrombin Tests. Am. J. of Clin. Path., **10**, 222, 1940.

19 Amberson, W. R.: Blood Substitutes. Phys. Rev., **12**, 48, 1937.

20 Hanzlik, P. J., and Karsner, H. T.: Anaphylactoid Phenomena from Intravenous Administration of Various Colloids, Arsenicals and other Agents. J. Pharm. Exp. Therap., **14**, 379, 1920.

21 Brunschwig, A., Scott, V. B., Corbin, N., and Moe, R.: Observations on the Intravenous Injection of Gelatin for Nutritional Purposes. Proc. Soc. Exp. Biol. and Med., **52**, 46, 1943.

22 Blalock, A., and Beard, J. W.: The Effects on the Composition of the Blood of the Subcutaneous Injection of Normal Salt Solution into Normal Dogs and into Dogs Submitted to Intestinal Trauma, Graded Hemorrhages, and Histamine Injection. J. Clin. Invest., **11**, 311, 1932.

23 Beard, J. W., Wilson, H., Weinstein, B. M., and Blalock, A.: A Study of the Effects of Hemorrhage, Trauma, Histamine, and Spinal Anesthesia on the Composition of the Blood when no Fluids are Injected and when Fluids are Injected Intravenously. J. Clin. Invest., **11**, 291, 1932.

24 Hoitink, A. W. J. H.: Treatment of Acute and Fatal Hemorrhage by Injection of Artificial Blood Substitutes: A Comparative Study of Artificial Blood Substitutes. Surg., Gynec. and Obst., **61**, 613, 1935.

25 Buttle, G. A. H., Kekwick, A., and Schweitzer, A.: Blood Substitutes in Treatment of Acute Hemorrhage: An Experimental Evaluation. Lancet, **2**, 507, 1940.

26 Harkins, H. N., and McClure, R. D.: The Present Status of Intravenous Fluid Treatment of Traumatic and Surgical Shock. ANNALS OF SURGERY, **114**, 891, 1941.

27 Hartman, F. W., Schelling, V., Harkins, H. N., and Brush, B.: Pectin Solution as a Blood Substitute. ANNALS OF SURGERY, **114**, 212, 1941.

28 Blalock, A.: Shock; Further Studies with Particular Reference to the Effects of Hemorrhage. Arch. Surg., **29**, 837, 1934.

29 Freeman, N. E., Shaffer, S. A., Schecter, A. E., and Holling, H. E.: The Effect of Total Sympathectomy on the Occurrence of Shock from Hemorrhage. J. Clin. Invest., **17**, 359, 1938.

30 Wiggers, C. J.: The Present Status of the Shock Problem. Physiol. Rev., **22**, 74, 1942.

31 Wiggers, C. J., and Werle, J. M.: Exploration of a Method for Standardizing Hemorrhagic Shock. Proc. Soc. Exp. Biol. and Med., **49**, 604, 1942.

32 Ebert, R. V., Stead, E. A., Jr., Warren, J. V., and Watts, W. E.: Plasma Protein Replacement after Hemorrhage in Dogs with and without Shock. Am. J. Physiol., **136**, 299, 1942.

33 Wiggers, C. J., and Werle, J. M.: Cardiac and Peripheral Resistance Factors as Determinants of Circulatory Failure in Hemorrhagic Shock. Am. J. Physiol., **136**, 421, 1942.

34 Wiggers, C. J.: Recent Studies on the Irreversibility Characteristics of Shock. Exp. Med. and Surg., **1**, 2, 1943.

[35] Trusler, H. M., Egbert, H. L., and Williams, H. S.: Burn Shock: The Question of Water Intoxication as a Complicating Factor: Blood Chemical Studies and Report of an Extensive Burn Treated by Repeated Transfusions of Blood and Blood Plasma. J. A. M. A., 113, 2207, 1939.

DISCUSSION.—DR. JOHN S. LOCKWOOD (Philadelphia, closing): I want to thank Dr. Graham for making reference to Hogan's work on gelatin. As a matter of fact, we have referred to it in the manuscript, but because of the shortage of time I omitted reference to it, which I would not have done had I been aware of the fact that that work was done in Cincinnati. Gelatin chemistry has made many advances toward purification and standardization of material, which gives us many advantages over workers of twenty-five years ago.

I also omitted reference in my remarks to the very interesting study being conducted by the group in Chicago, under Dr. Brunschwig. We feel that these two studies are supplementing each other in a very useful way. We also believe that gelatin may serve as a means of providing parenteral feeding of protein.

One of the problems we have been up against all along in this work has been to "hew to the line" of studying gelatin as a blood substitute, because so many interesting problems concerning shock and burns have cropped up in connection with the work, that we have been tempted frequently to drop our primary study in pursuit of these possible "will-o'-the-wisps." For example, we think the gelatin work has brought out further evidence of the dissociation of the problem of blood-volume maintenance from the problem of peripheral blood flow in the shocked individual.

The restoration of normal blood volume by the administration of a colloid such as gelatin will not alone constitute adequate therapy in shock.

PROBLEMS OF PROTEIN NUTRITION IN BURNED PATIENTS*

F. H. L. Taylor, Ph.D., Stanley M. Levenson, M.D.,
Charles S. Davidson, M.D., Newton C. Browder, M.D.,
and
Charles C. Lund, M.D.
Boston, Mass.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), and the Burn Assignment of the Surgical Services of the Boston City Hospital and the Departments of Medicine and Surgery, Harvard Medical School, Boston, Mass.

Although the treatment of the burned patient is usually regarded as a surgical problem, numerous underlying physiologic, metabolic and clinical complications must be constantly borne in mind. Frequently, the success or failure of carefully planned and well executed surgical procedures, such as skin grafting, depends upon the early recognition and effective handling of these underlying disturbances. Infection,[1] shock, immediate or late,[2] anemia,[3] and disturbances of kidney or liver function[4] may occur as complications of burns. All these factors tend to delay healing.

The presence of any, or all, of these factors may also have a profound effect on the metabolism of the patient. An opportunity has been afforded to study some of the abnormalities of metabolism in a large series of burned patients. The details of the earliest of these investigations are given elsewhere.[5] The present communication deals with only one aspect of this very large problem, namely, the problem of protein metabolism in the burned patient.

Hypoproteinemia occurred frequently in a series of 63 patients upon whom a sufficient number of laboratory observations were made. In some patients, hypoproteinemia was fugitive, and was probably associated with early loss of plasma. In others, it persisted for some time, but was not severe and responded to high protein diets containing from 100 to 125 Gm. of protein per day. These diets were supplemented with 25 to 30 Gm. of brewers yeast† and other added vitamin supplements,‡ and contained approximately 3000 calories. Other patients did not respond to, or could not ingest, such diets. This group was composed of the most severely burned of all the patients studied, and in them the hypoproteinemia became progressive, and often reached the anasarca level. Simple loss of plasma in the form of persistent surface exudate could not alone account for the hypoproteinemia

* Presented before the American Surgical Association, Cincinnati, Ohio, May 14, 1943.

The work described in this paper was done, in part, under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

† Provided by the courtesy of the Brewery Foundation, of New York.

‡ Provided by the courtesy of Merck & Co., Rahway, New Jersey.

in these patients. But there is no doubt that this was an important contributing factor, although, unfortunately, one that cannot be studied quantitatively.

A detailed study of nitrogen metabolism has been made upon a patient with a burn of 55 per cent of his body surface. Similar studies have been made upon nine other patients. The data from these patients are not complete but are entirely confirmatory in essential details of the findings reported here. The important laboratory data are presented in Chart 1. All values have been calculated in terms of protein. They include protein intake from all sources.

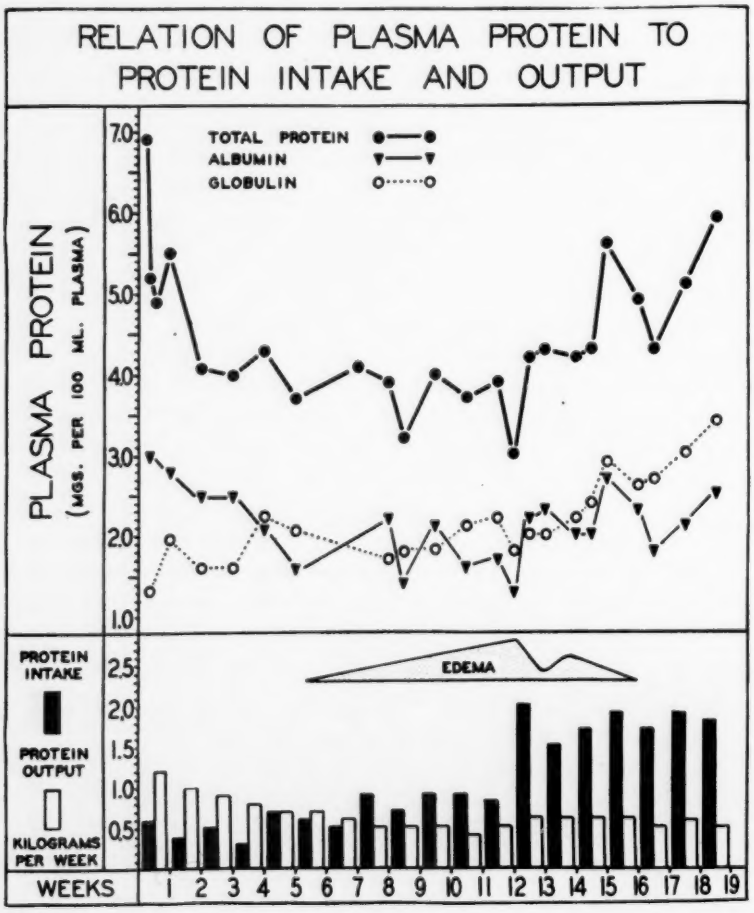


CHART I

CASE REPORT

C. J., age 22, a coast guardsman in excellent physical condition and with a noncontributory past history sustained flame burns shortly before entry to the hospital. On admission, a physical examination revealed a well-developed and well-nourished

young man, with burns of such severity that it was later determined that approximately 45 per cent of his body area was involved in third degree burns and a 10 per cent further area with second degree burns. The burns were on the face, scalp, whole back, flanks, and large parts of all four extremities.

His pulse was rapid and thready. He was cold and clammy. His blood pressure was not taken because of his leg and arm burns. Marked hemoconcentration was present and the required 17 units* of plasma were administered based both on the extent of the burn and on hematologic data. The plasma and four liters of saline were administered over a period of 48 hours, all of the plasma being given in the first 24 hours. No débridement was attempted, and his burns were treated by triple dye.

His early complications were hemoglobinemia, hemoglobinuria, with oliguria and azotemia. His azotemia was of a reversible type. The blood nonprotein nitrogen returned to normal after a few days of normal urine output. At the end of 24 hours he was given sulfadiazine by mouth, with satisfactory blood levels and a normal kidney clearance of the drug.

Urine nitrogen data showed the presence of unusually large amounts of nitrogen in the urine, amounting on some occasions to 34 Gm. in a 24-hour period. He lost his appetite and, for a period of four weeks, the protein component in his diet did not exceed 80 Gm. per day. At the end of six weeks he had sustained a calculable net loss of over 2000 Gm. of protein. This deficit was occasioned by the negative nitrogen balance occurring during the first four weeks. These figures obviously do not take into consideration the very considerable loss of nitrogenous material from the burned area which, by clinical observation, persisted for 19 weeks, at which time the skin grafting was nearly complete. Therefore, the nitrogen deficit must actually have been much greater than the calculable 2000 Gm. would indicate.

The significance of a protein deficit of 2000 Gm. should be carefully examined. It represents an equivalent in terms of plasma of 40,000 Ml. Expressed as loss of muscle tissue, it represents a loss of ten kilograms, or approximately 22 pounds. The problem of balancing such a protein deficit in a severely burned patient by feeding a high protein diet was extremely difficult. By considerable persuasion, the patient was prevailed upon to take many supplementary feedings until his intake was approximately 130 Gm. of protein a day, and his caloric intake 3000 Gm. This represented in his case the absolute physical ability of the patient to ingest food by mouth. This diet was continued from the 7th to the 12th week of his hospital stay. From the end of the first week he also had another small source of protein intake in the plasma content of 6000 cc. of whole blood transfusions in 12 weeks. These were given in 300–1000 cc. doses at frequent intervals. The plasma proteins from this source is included in the values given in the chart. Nevertheless, in spite of cooperation on the part of the patient, and in spite of the fact that an *apparent positive nitrogen balance* was obtained throughout this period of high protein intake, his plasma protein fell and the edema, which became noticeable at the end of the fourth week, progressed. By the beginning of the 12th week the plasma proteins had fallen to 3.1 and the albumin to 1.6 mg. per Ml. of plasma, respectively, and the edema was massive.

His clinical condition at the beginning of the 12th week was desperate and heroic measures of alimentation were begun. Seventy-five Gm. of human albumin† and several units of desiccated plasma, reconstituted at ten per cent protein content, were administered and feeding commenced by vein and stomach tube. The details and

* One unit of plasma is 250 ml. of therapeutic plasma with a protein content of approximately five per cent.

† Provided through the courtesy of Professor E. J. Cohn.

theoretic discussion of the alimentation used in this patient is given in another communication.[6] Only the essentials of the treatment will be given here. The protein intake was increased from 800 Gm. to between 1700 and 2000 Gm. per week. On some days his protein intake amounted to 500 Gm. Intravenous alimentation was carried out with amino-acids obtained from acid hydrolysis of casein with added water-soluble vitamins. By stomach tube, a high caloric, high protein, high vitamin diet in semifluid form were administered. The intubated food was supplemented with 30 to 40 Gm. of brewers yeast, 20,000 units of vitamin A, 1000 units of vitamin D, 200 mg. of asorbic acid, 20 mg. of thiamin, 10 mg. of riboflavin, and 200 mg. of nicotinamide per day. The nitrogen intake per week administered by vein was equivalent to 225 to 625 Gm. of protein, while by intubation over the same period of time from 1000 to 1200 Gm. of protein were administered.

The results were striking. Immediately following the administration of the albumin and concentrated plasma there was an abrupt delivery of the edema, which continued to diminish in degree throughout the first week of high protein intake. During the second week of forced alimentation the edema reappeared briefly, due, in part, to an error in making up the amino-acid solution in isotonic saline, instead of in distilled water. About 10,000 Ml. of saline solution were thus administered over a period of four days before the error was detected. However, the correct procedure was reestablished and the edema gradually decreased until, by the beginning of the 15th week, it disappeared. The forced alimentation was continued until the end of the 19th week.

In the 14th week his general appearance and the appearance of his granulating surface had improved to such an extent that for the first time since the burn it seemed possible to perform skin grafting operations. Because of the great area involved, Reverdin grafts were chosen as the only reasonable kind. During the next four weeks he underwent, in bed, four three-hour sessions of grafting. Novocain anesthesia was used. The growth of new skin between the grafts was exceptionally rapid.

The total plasma protein rose from the 12th to the 19th week to an almost normal level. Following the administration of albumin, there was an abrupt rise in the plasma albumin fraction. The loss of edema during the day following the administration of albumin was striking. It may also be mentioned that there was a slow rise of globulin from the 12th week on. The rise continued and resulted in an abnormally high globulin level. The cause of this rise is not at present known. Liver function tests at this time were normal although infection was present.

At the conclusion of the period of forced alimentation, it was calculated that a positive balance of 6000 Gm. of protein existed in this patient. However, partition of the blood and urine nitrogen showed no remarkable loss of amino-nitrogen when amino-acids were injected. Neither was the total nitrogen of the urine remarkably increased. In fact, on one day, when the intake was calculated as 500 Gm. of protein, the patient retained approximately 380 Gm. and the urine nitrogen excretion showed a 75 per cent conversion of all excreted nitrogen to urea. It would appear, therefore, that the loss of nitrogen through the granulating surface or the demand for tissue must have been very great, since, while the calculated nitrogen deficit based on intake and output studies was more than balanced by forced alimentation, he continued to metabolise and to retain large amounts of protein.

The clinical improvement of the patient under this regimen was striking. In the 19th week he was returned to a diet of 125 Gm. of protein without noticeable return of edema. In the 23rd week he was weighed for the first time since the accident. Although his health and appearance had improved greatly from his worst condition, he was still 55 pounds below his normal 167.

Discussion.—The findings in this patient, and in the eight other patients studied, are confirmatory of the observations of Lucido.[7] In severely burned patients there appears to be an excessive loss of nitrogen into the urine in addition to large losses of nitrogen by exudation from the burned surface, and an increased nitrogen demand for the building of new tissue. These three factors can result in serious nitrogen deprivation, with consequent edema and general malnutrition. The causes of increased nitrogen loss are many. Tissue destruction, infection, increased metabolism and demand for protein for the repair process all play a part.

It must be emphasized that, while the majority of burned individuals may restore nitrogen balances on simple dietary regimens, severely burned patients may not. There was a direct relation between the extent and severity of burn and the amount of nitrogen loss in the present series of cases.

Nitrogen balance studies based upon urine and stool analyses, together with known nitrogen intake, cannot reveal the quite considerable nitrogen loss from the burned surface and the demand for building new tissue. On a high protein diet alone, this patient developed a protein deficit of 2000 Gm., based upon intake and output studies, which was eliminated and a final, apparent, positive balance obtained. In spite of this, the patient's edema increased and it was not until a total nitrogen retention estimated at over 6000 Gm. of protein had been obtained that the edema was completely delivered and a good nutrition obtained. In other words, at least 6000 Gm. of protein were required, over and above that indicated by balance studies by this patient, and this only after the net loss of 55 pounds of his original body weight.

These results suggest that an early appraisal of nitrogen losses in burned patients is necessary. When marked negative nitrogen balances appear, steps must be taken to provide an enhanced nitrogen intake. In some severely burned patients positive nitrogen balances will be found impossible to maintain from diets alone, due to the physical impossibility of ingestion of such diets. In such an event, it is suggested that forced alimentation by intubation or by the intravenous administration of amino-acids, with the precautions previously stated,[5] should be attempted as soon as possible.

With such protein deficits as shown here, replacement by whole blood or plasma transfusions are clearly impossible, since it would be necessary to administer 120 liters of plasma to accomplish the equivalent of the supplementary alimentation given. The only satisfactory way that can be considered at present is forced alimentation by intubation and amino-acid administration by vein with proper precautions.

SUMMARY AND CONCLUSION

1. Increased nitrogen excretion in the urine of some severely burned patients has been established.

2. Calculable nitrogen deficits, based upon intake and output studies alone, of some duration and great magnitude have been observed.

3. Correction of such a deficit by high protein feeding failed to bring a patient into true nitrogen balance because of incalculable losses which were probably from the burned and granulating surface.

4. Heroic intravenous and tube feeding apparently restored his true protein balance. This feeding reached a level of intake of the equivalent of 2000 Gm. of protein per week, and resulted in establishment of an apparent positive nitrogen balance of over 6000 Gm.

5. In spite of this apparent positive nitrogen balance, he is still more than one-third below his normal weight, so that even the calculation and considered deficits are much below the actual one.

The authors acknowledge the technical assistance of the Laboratory Staff of the Thorndike Memorial Laboratory and of the Burns Assignment. They also express their gratitude to the Surgical Staff and the Special Diet Kitchen of the Boston City Hospital, without whose cooperation this study could not have been made.

REFERENCES

[1] Harkins, H. N.: The Treatment of Burns. Review Article, Chap. 9 and 10, Baltimore, Charles C. Thomas, 1942.

[2] Blalock, Alfred: The Importance of Local Loss of Fluid in the Production of Low Blood Pressure After Burns. Arch. of Surg., **22**, 610, 1931.

[3] Beckey, K., and Schmitz, E.: Klinische Beitrage zur Pathologie der Verbrennung. Mitt. a.d. Grenzgeb. d. Med. u. Chir., **31**, 416, 1918–1919.

[4] Wilson, W. C.: Systemic Disturbances in Extensive Burns. Brit. Med. Jour., **2**, 679, November, 1940.

[5] Taylor, F. H. L., Levenson, S. M., Davidson, C. S., and Adams, M. A.: Abnormal Nitrogen Metabolism in Patients with Thermal Burns. (In preparation.)

[6] Davidson, C. S., Levenson, S. M., and Taylor, F. H. L.: The Problem of Alimentation in Individuals with Severe Thermal Burns. (In preparation.)

[7] Lucido, Joseph: Metabolic and Blood Chemical Changes in a Severe Burn. ANNALS OF SURGERY, 111, 640, 1940.

DISCUSSION.—DR. LELAND S. MCKITTRICK (Boston): Doctor Allen asked me if I would pinch-hit for him. I feel totally inadequate to discuss any one of these three papers. Doctor Allen felt, however, that it might be of some interest, as a part of this discussion, to summarize briefly the results at the Massachusetts General Hospital on the patients from the Cocoanut Grove disaster. When he found he had to leave town, he handed me this slip of paper on which were some figures given to him by Dr. Oliver Cope, who had taken a very active part in all the work of this group of patients.

There were 114 casualties brought to the Massachusetts General Hospital in the period of about an hour and a half. There were a few stragglers after that, but not very many. Fifty-five of those were dead on arrival, and within 15 minutes another 20 died, making a total of 75 deaths out of the 114 patients. Thirty-nine patients were admitted for treatment.

The hospital was particularly well suited to handle a group of this size. One surgical floor was completely evacuated, and these 39 patients were promptly sent to this floor.

These burns all followed a pretty uniform pattern—face, hands and trunk were

burned. It was apparently a flash-type of burn, and practically all of them had some type of pulmonary complications. Many of them had pretty severe burns of their upper respiratory trees. There was little or no burn shock, possibly because of, or in spite of, the fact that it was a cold night; they were all wet; and many of them had been out in the cold for a matter of 20 or 30 minutes before they had arrived at the hospital. There were no associated injuries of any kind, no fractures, no open wounds. It was purely the burn and its associated problems.

Doctor Churchill felt that this should be an ideal group to try a method of treatment which he had come to believe was well suited to burns of this type. There was no débridement. There was no cleaning. A simple boric ointment dressing and pressure were applied to wherever the burns might have been. On the faces, nothing but the nose and mouth were left open. Those who were not sensitive were given tetanus antitoxin. Sodium sulfadiazine was given to all of them. In this connection, it is interesting to note that the bleb fluid contained the same level of diazine as did the blood. The slough of the deep burns contained organisms, but there was no cellulitis, lymphangitis, or lymphadenitis.

It was felt that the isolation of this group of patients was about as complete as could be obtained. Visitors were not allowed. Nobody was allowed on the floor except those actively associated with the care of the patients. Even a lot of men who had spent all night treating burns were not allowed to go in and follow the cases. Everybody who had to do with the patients was masked and, so near as possible, the strictest aseptic precautions were carried out.

Now as to the results. Of the 39 patients, seven died. Within the first 12 hours, there were no deaths. The seven deaths occurred from 13 to 62 hours—all of pulmonary complications. At the end of 42 days, one of the men committed suicide.

There were seven patients who had from 50 to 70 per cent of their bodies burned, and of those seven, four lived. Nearly all patients had some degree of pulmonary complications; five requiring tracheotomy. Three of these died.

As Doctor Whipple said, and as would be expected, the second degree burns healed very promptly. Seventeen of the 39 patients were discharged from the hospital by the end of two weeks.

Nine of the ten patients with deep burns required extensive skin grafting. All of the patients have now left the hospital.

There were two or three points which are worthy of note. Without any question, we gave some of these people too much morphine. We misunderstood the restlessness and the mania of anoxia for pain, and in two or three occasions morphine was probably given to a hazardous degree. It was the feeling of Doctor Beecher, and, I think of all the group, that the barbiturates, in many instances could have been employed with much greater safety. Care must be taken not to give excessive salt, especially if normal saline is used to dilute the plasma.

After a review of these patients, it was our feeling that, for a group of casualties such as this, the method of treatment employed had certain definite advantages: It was simple; could be easily applied by less skilled personnel; permitted early application, thus minimizing contamination; and did not interfere with the treatment of shock or anoxia. I think we were all impressed with how quickly they became comfortable and how little medication was required to keep them so.

Dr. Robert Elman (St. Louis): The war and other catastrophies often give a ray of light to physicians and investigators, because it stimulates and gives opportunity of learning a good deal more about the various injuries and difficulties with which we are confronted. I think this is important, and Dr. Whipple has emphasized the fact that we are now learning a great deal more about burns than we ever did before. This point should be emphasized because at no time in the treatment of any condition should we ever rest on our laurels and think that the problem is finished.

To anyone who has tried to prepare extensive full-thickness third degree burns for skin grafting, the problem of nutrition is a very real one, and yet it is frequently overlooked. The observations of Dr. Lund, and his collaborators, have added much to our knowledge of the mechanism of the nitrogen loss in these severely burned patients, and I hope that their further studies may reveal the cause of this excessive loss, so that it may be prevented. Until this occurs, however, we must treat this nitrogen loss by increasing tremendously the nitrogen intake with high protein feedings. The magnitude of this increase is well shown by the high protein diets given their patients. That they were successful is indicated by the fact that they were able to give one of their patients *in one day* as much as 500 Gm. of protein, a nutritional feat which to me could be described as a therapeutic triumph.

It might be mentioned, of course, that an ounce of prevention is often worth a pound of cure, and that if one starts the high protein and high caloric intake as early as possible after the burn, much of the protein deficiency can be prevented. In one of our cases, the kodachrome of which is presented herewith, (taken on the 34th day), we started our high protein diet within the first week after the burn, in fact, as soon as the vomiting stopped. This was more than a 40 per cent full-thickness burn and, as you can see, the granulating area is free of slough and clean. She was treated by rapid coagulation with tannic acid and silver nitrate. I attribute part of her excellent general condition to the fact that she was very fond of chocolate malted milk and ice cream, and this was given her practically day and night. She probably ingested as much as five Gm. of protein per kilo per day, although we do not have the exact figures. This does not reach the record established by Dr. Lund, which is almost ten Gm. of protein per kilo per day.

Dr. Evarts A. Graham (St. Louis, Mo.): I have nothing very much to add to the discussion, except that I wonder if Doctor Lockwood is familiar with the work of Doctor Hogan on the use of gelatin, which was published about the year 1912. Doctor Hogan was a pupil of Dr. Martin Fisher, who is Professor of Physiology at Cincinnati.

This work was done before blood transfusions had reached a practical stage. It seemed that the promise of gelatin as a medium which could be used in the treatment of shock in place of the impractical blood transfusion at that time, might answer a very difficult problem which confronted surgeons.

The difficulties which confronted Doctor Hogan, however, were, first of all, I think the difficulty in having a gelatin which was nontoxic, but, at any rate, in his experimental animals he got results from the use of gelatin which seem to be very promising indeed.

Lt. Comdr. Maurot, M.C. (Norfolk, Va.): As one member of the burn team at Norfolk General Hospital, I have helped to treat all the burns received there during the past seven months. We have met with all the problems outlined so excellently by Doctor Lund. During this time, we have tried to combat the hypoproteinemia with plasma, and have been unsuccessful. We also had difficulty in feeding a sufficiently high protein diet to a patient to have their protein reach a point of six to eight per cent.

Doctor Lund spoke of hypoproteinemia and also the terrific anemia seen in these cases. In some cases we have seen a burn case having red blood count of four million fall to two and a half million in four days. We cannot explain this terrific anemia in such a short time. We have not seen any cases of jaundice, nor any cases of hemoglobinuria; and we have not been able to prove, as some writers have stated, that there is an increased fragility of the red blood cells.

There is one point I wish to bring out on skin grafting. We attempt to graft our burns as soon as possible; if feasible, between the tenth and fourteenth day after the initial injury. In some of our cases in which the burned area is more than 50 per cent, it has been difficult to find areas of skin from which to graft, so we have developed the following technic, which, however, is not original, although there is nothing in

the literature upon it: We take a section of skin approximately an inch and a half wide and three inches long, the full-thickness of skin, shave all the fat from the under surface of it, and divide the skin into two portions, giving us two pieces of skin approximately three inches long and approximately three-quarters of an inch wide. We then shave the full-thickness grafts, each of which are about three-quarters of an inch wide and approximately a thirty-second of an inch thick. The donor area is closed by interrupted sutures. From a piece of skin of this size, we can obtain approximately 200 small pinch grafts, and the donor area can be sutured, closed, and held by primary means.

In other grafts that we did originally, using Thiersch's or intermediate-thickness grafts, the donor area will not heal and usually becomes infected, or in other words, you are merely "robbing Peter to pay Paul"—you take skin from the thigh to place on the arm, and then the thigh will not heal and you have to graft it.

DR. ALEXANDER BRUNSCHWIG (Chicago): We have been interested in gelatin also from the standpoint of parenteral nitrogenous nutrition. It has been possible to maintain dogs in positive nitrogen balance 12 days or more with daily injections of gelatin, dogs who take little or no protein by mouth. It can be used in man, but the real value of its use in man, of course, has to be determined. There is no question about its safety. We have given it in doses of 100 to 150 cc. of ten per cent solution daily for 12 days, supplementing light diet by mouth, without any reactions. As much as 300 cc. of a ten per cent solution of gelatin has been given intravenously, in a short time, to patients without reactions. We have given it to patients for periods of four to five days, followed by a rest period of 10 to 12 days, and then resumption of injections, without observing acquired sensitivity.

In contemplating studies with gelatin, one has to choose the source. There are several kinds: there is hog or calfskin gelatin, bone gelatin, and fish swim-bladder gelatin. They are made in various ways by different manufacturers. As they come from the manufacturer, a ten per cent aqueous solution may gel at room temperature, but autoclaving for 45 minutes or an hour affords a solution that will not gel until much lower temperatures are reached (–8° C., or lower).

I think it offers a very interesting substance with which to work. It is not a complete protein, but by supplementing it with the missing amino-acids it may prove to be a very valuable substance for intravenous feeding. It is easily available, very cheap, and very easy to handle.

DR. CHARLES C. LUND (Boston, closing): The caloric intake is very important in giving a high protein diet. If a high protein diet is given without plenty of carbohydrate, some of the protein has to be used for fuel.

During the period of highest protein intake, when this man turned the corner, his caloric intake was about 6000 calories per day. During fairly long periods of time, the intravenous amino-acids made up about a third of his nitrogen intake. More can be used if the veins will stand it. In fact, complete nitrogen balance in patients, who do not demand as much nitrogen as these patients do, can be achieved by intravenous treatment alone. There are reactions. I think there are reactions with all available kinds of amino-acids at present, but they are not terribly serious.

I disagree with my friend, Dr. Koch, about one point, in his final three-point statement of the all-important things in burns. One of the points was the prevention of infection. Now, when you have a burn with deep, extensive, third-degree loss, you are going to get colon bacilli and staphylococci in the area, no matter what treatment. Complete prevention of infection is beyond human capabilities at present. I think Dr. Koch will agree with this. Therefore, think about how to treat this inevitable infection. The best program we can offer is to treat the infection indirectly, by supporting the patient so that he can withstand the infection. That is a principle that goes back for ages. Shattuck, for instance, at Massachusetts General Hospital, in 1897, published a paper on "The Increased Feeding of Patients with Typhoid Fever." His results were

not spectacular, but the principle was absolutely sound, and his results did show a definite improvement.

I am very much interested in Dr. Maurot's comments, and I hope he will continue his efforts by using the stomach tube. Dr. Whipple has suggested the use of a Miller-Abbott tube.

We used to think one could not undertake grafting until the infection was cleaned up in the whole area. We have started recently, putting small Thiersch grafts onto granulation tissue as soon as a small area of it is free of slough, in spite of there being dying foul-smelling slough very closely adjacent to this area. If the patient's nutrition is right, such grafts, completely surrounded by infection, with the help of a little sulfanilamide perhaps, will take.

AMINO-ACIDS, SERUM AND PLASMA IN THE REPLACEMENT THERAPY OF FATAL SHOCK DUE TO REPEATED HEMORRHAGE*

AN EXPERIMENTAL STUDY

ROBERT ELMAN, M.D., AND CARL E. LISCHER, M.D.

ST. LOUIS, MO.

FROM THE DEPARTMENT OF SURGERY, WASHINGTON UNIVERSITY MEDICAL SCHOOL, AND BARNES HOSPITAL, SAINT LOUIS, MO.

IN PREVIOUS STUDIES from this clinic it was shown[8, 9, 11] that the amino-acids of hydrolyzed protein are effective as a parenteral method of correcting hypoproteinemia of nutritional origin. In view of the obvious practical advantages of such solutions over plasma, it was natural to try their possible therapeutic value in the acute hypoproteinemia which follows severe hemorrhage. In this communication are described experimental studies on fatal shock produced by repeated hemorrhage, in which replacement of the lost blood by an amino-acid mixture seemed to have a beneficial effect. A preliminary note has already been published.[12]

Extensive experiments, of course, have dealt with the production of surgical shock by hemorrhage,[13, 25] many by members of this Association.[1, 17, 20] However, in the present experiments the approach has been, to a large extent, biochemical rather than physical or physiologic. This deserves emphasis, inasmuch, as amino-acid mixtures can in no real sense be classed as a blood substitute because they lack the colloidal properties of blood plasma. The value of such injections, if they have value, must depend upon the ability of the body to use amino-acids to synthesize plasma proteins rapidly, or for nutritive or other metabolic purposes. Nevertheless, comparative experiments were carried out with serum and plasma.

Considerable evidence that protein metabolism is a rapid procedure emerges from the important work[22] with isotopic nitrogen. Other workers[2] have recently shown that similarly labeled amino-acids appear in plasma proteins within an hour after injection. These fundamental studies indicate that it is theoretically possible for injected amino-acids to be made into plasma proteins very rapidly, and thus act as an indirect substitute or supplement to plasma. Undoubtedly, the liver is the key organ in this process and we shall have some evidence to show that this is the case.

EXPERIMENTAL PROCEDURES

Because surgical shock involves so many variables, we adopted a method which seemed to give a relatively uniform response. Instead of basing our experiments on the level of hypotension or the amount of hemorrhage, we subjected dogs to uniform repeated bleedings (10 cc. per kilogram of body weight each hour) until death ensued, and then used the survival time as the basis for measuring the effect of various replacement procedures. Systolic

* Aided by a grant from the Commonwealth Fund.

Read before the American Surgical Association, May 13-14, 1943, Cincinnati, Ohio.

blood pressure as well as hematocrit and fractional plasma proteins were also determined. General anesthesia was not used. The effect of changes in posture was avoided by carrying out the entire experiment while the animal was in the supine position.

Unselected mongrel dogs, varying in weight from 7 to 19 kilograms, were given water *ad libitum,* but no food during the 18 hours preceding the beginning of each experiment. A cannula was inserted into the femoral artery and bleeding carried out as rapidly as possible; the calculated amount usually being obtained within a minute or two. The systolic blood pressure was recorded before and after each hemorrhage with a Tycos manometer[7] connected to the same cannula used for bleeding. For hematocrit and fractional plasma protein determinations, samples of heparinized venous blood were taken immediately preceding each hemorrhage. The former was measured after centrifugalization at 3000 R.P.M. for 30 minutes. Supernatant plasma was drawn off; the nonprotein nitrogen estimated by nesslerization, fractionation carried out,[4] and nitrogen determined by a Kjeldahl procedure.[23]

The therapeutic value of the various solutions tested was compared by using them to replace the blood removed after each hemorrhage. The fluids for replacement were sterile, but no attempt at complete asepsis was made during the experiment because of its short duration. The injections were rapid and followed immediately each bleeding, the volume being exactly equal to the volume of blood removed. In most experiments the fluids were injected into the femoral artery through the same cannula used for bleeding, but in a few groups the fluid was introduced into the adjacent femoral vein.

Seven groups of experiments were carried out as follows:

TABLE I

	No. of Dogs	Replacement Fluid
Group I	10	None.
Group II	20	10% glucose in normal saline solution.
Group III	6	Pure amino-acids 5%, glucose in normal saline 5%.
Group IV	20	Protein hydrolysate 5%, glucose in normal saline 5%.
Group V	10	Dog serum diluted with an equal quantity of 10% glucose in normal saline.
Group VI	10	Citrated dog plasma diluted with an equal quantity of 10% glucose in normal saline.
Group VII	10	Heparinized dog plasma diluted with an equal quantity of 10% glucose in normal saline.

The protein hydrolysate* was an enzymatic digest of casein (Amigen) or beef serum. No difference was observed in the results with these two hydrolysates. The pure amino-acids† consisted entirely of essential amino-acids.[21] Both solutions were neutralized with sodium hydroxide to a p_H of 6.5 to 7.5. The nitrogen content of the two was similar, *i.e.,* 0.66 and 0.63 gm. per cent, respectively. Serum was obtained by centrifuging clotted dog blood; in some cases it was fresh and in others it had been stored for two weeks at freezing temperatures before separation; no obvious difference was

* Supplied through the courtesy of Dr. Warren M. Cox, of Mead Johnson and Co.

† Supplied through the courtesy of Dr. D. F. Robertson, of Merck and Co.

observed in the effects of these two methods of preparation. The citrated plasma contained about 0.6 gm. per cent of sodium citrate. To obtain the heparinized plasma one-half cubic centimeter of heparin solution (Lederle) was added to each 1000 cc. of whole dog blood.

It should be pointed out that dilution of whole plasma and serum was necessary, so that the actual amount of plasma protein replaced was roughly the same as that removed. An equal amount of diluting fluid was used because the average red cell volume was 50 per cent. Constancy of the plasma proteins was insured by using pooled plasma from many dogs.

At the termination of each experiment a microscopic section was made of the liver. In a separate series of six dogs, a biopsy of the liver was removed under nembutal anesthesia two hours before the initial bleeding and at death. In three of them glucose was used as replacement, and in the other three hydrolyzed protein.

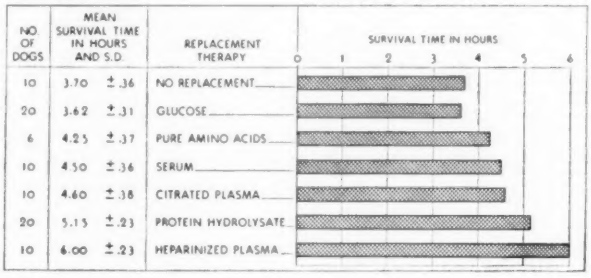

NO. OF DOGS
MEAN SURVIVAL TIME IN HOURS AND S.D.
REPLACEMENT THERAPY
SURVIVAL TIME IN HOURS
0 1 2 3 4 5 6
10 3.70 ±.36 NO REPLACEMENT
20 3.62 ±.31 GLUCOSE
6 4.25 ±.37 PURE AMINO ACIDS
10 4.50 ±.36 SERUM
10 4.60 ±.38 CITRATED PLASMA
20 5.15 ±.23 PROTEIN HYDROLYSATE
10 6.00 ±.23 HEPARINIZED PLASMA

FIG. 1.—Survival-Times in the Seven Groups of Experiments Described in the Text: S. D. = Standard deviation, calculated according to usual statistical formulae. Note that replacement with heparinized plasma and a protein hydrolysate gave the longest survival time, and the relatively poor showing with serum and citrated plasma.

EXPERIMENTAL RESULTS

The first observation of interest was that removal by repeated bleedings of an average of but 43 cc. per kilo of blood led to an invariably fatal outcome; by contrast, survival is frequent when the same amount of blood is removed in a single hemorrhage. This has been the experience of other observers and we have performed single hemorrhages of this magnitude with a mortality of but 20 per cent.[9] Clinical observations are similar, in that patients often survive a single bleeding, but are apt to succumb after subsequent though smaller ones. This is especially true of war wounds, for even if there has only been a single initial hemorrhage, further bleeding is sure to occur during débridement.

Survival Time.—Of greater importance was the observation (Fig. 1) that replacement with 10 per cent glucose in normal physiologic saline had no influence on the survival time, in contrast to the results with the solution containing hydrolyzed protein, in which the survival time was

5.1 hours, as compared with 3.6 hours for the controls.* The experiments with pure amino-acids were only six in number, but the results (survival time = 4.2 hours) were only somewhat better than with glucose (survival time = 3.6 hours), indicating that the greater effect of the hydrolyzed protein on survival time could not have been due to the mere presence of amino-acids *per se*.

Of special significance were the comparable experiments in which serum, citrated plasma and heparinized plasma were used for replacement. The first two fluids produced no greater survival time than was obtained with the

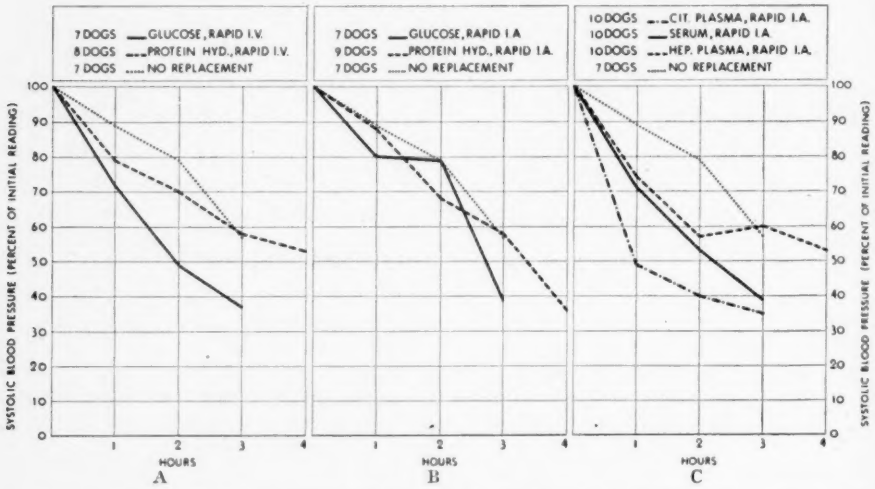

7 DOGS — GLUCOSE, RAPID I.V.
8 DOGS --- PROTEIN HYD., RAPID I.V.
7 DOGS ..... NO REPLACEMENT
7 DOGS — GLUCOSE, RAPID I.A.
9 DOGS --- PROTEIN HYD., RAPID I.A.
7 DOGS ..... NO REPLACEMENT
10 DOGS -.- CIT. PLASMA, RAPID I.A.
10 DOGS — SERUM, RAPID I.A.
10 DOGS --- HEP. PLASMA, RAPID I.A.
7 DOGS ..... NO REPLACEMENT
SYSTOLIC BLOOD PRESSURE (PERCENT OF INITIAL READING)
HOURS
A
B
C

FIG. 2.—Blood Pressure Response: The curves were drawn from mean values in groups of dogs surviving at least three or four hours, but does not include the terminal fall. The curve in which there was no replacement is shown in all of the above three graphs.

A. Note pronounced fall during intravenous replacement with glucose as compared with hydrolyzed protein.

B. With intra-arterial replacement the difference noted in A is the same, but not as pronounced.

C. Note the precipitate early fall with citrated plasma. Serum showed the same though somewhat delayed drop. Heparinized plasma, after two hours, maintained a good level of pressure.

hydrolyzed protein. The heparinized plasma, on the other hand, resulted in the longest survival time (six hours).

Of some interest is the fact that no differences were observed in the survival time between experiments in which the fluid was replaced intravenously as compared with those in which they were injected intra-arterially. This topic has been the subject of previous investigations.[6, 15, 16]

Blood Pressure Response.—A progressive fall in blood pressure was observed in each group of experiments as shown in Figure 2. In general, the behavior of the blood pressure was somewhat variable, an observation made by others. In many instances the drop after each hemorrhage was pronounced but recovery good, whereas, in others the blood pressure was

* That this difference is statistically significant is shown by dividing the difference of the means by the standard deviation of the difference. When the figure thus obtained is used in consulting statistical tables, it becomes a certainty that this difference is not a chance phenomenon.

maintained rather well but then dropped abruptly before death. Nevertheless, the average values obtained in similar groups of experiments show significant variations which in most instances can be correlated with the survival time. For example, the greatest blood pressure drop was exhibited by the dogs in which citrated plasma was used, whereas, with the heparinized plasma the blood pressure was sustained after a drop in the first two hours. Moreover, the hydrolyzed protein was followed by a definitely higher blood pressure than similar experiments with ten per cent glucose, particularly when replacement was intravenous rather than intra-arterial. Quite surprising was the fairly good blood pressure, until the terminal fall, in dogs bled with no replacement.

Red Cell Volume and Plasma Proteins.—A progressive fall in red cell volume, plasma albumin, and globulin was observed in all experiments, although there were definite and significant differences between the different groups. For purposes of simplification, presentation of this data is limited to that shown in Table II. Therein, are figures representing the observations made three hours after the beginning of the experiment, *i.e.*, after each animal had lost 30 cc. per kilo, and just before the fourth hemorrhage was carried out. The numbers refer to the fall in value expressed as a percentage of the initial determination. For example, the experiments in which pure amino-acids were used for replacement at three hours showed a drop in hematocrit to 98 per cent, in albumin to 83 per cent, and globulin to 88 per cent of the initial value.

TABLE II

	Hematocrit	Albumin	Globulin
Pure amino-acids	98	83	88
No replacement	94	90	94
Hydrolyzed protein	88	81	75
Glucose	83	74	71
Heparinized plasma	79	83	81
Citrated plasma	75	77	79
Serum	85	85	94

The importance of this data on plasma proteins and red cell volume lies in the fact that they measure the factors influencing fluid shift and colloidal osmotic pressure, which, as discussed in a previous paper,[9] control these compensatory mechanisms following hemorrhage. In other words, restoration of blood volume from extracellular fluid (hemodilution) is indicated by the fall in the hematocrit, while the addition of the two plasma proteins to this diluting fluid, particularly albumin, which contributes 85 per cent of the colloidal osmotic pressure of the blood, is indicated by the comparative changes in their relative concentrations.

Pathology.—At autopsy, the bloodless condition of the tissues was a uniform finding. The viscera were pale and in no instance was any engorgement or congestion of the intestines observed. Study of microscopic sections of the liver were of greatest interest, and showed in general a shrinking or diminution of stainable cytoplasm. This was less pronounced in the dogs

receiving hydrolyzed protein as compared with those getting glucose as replacement (Figs. 4, 5 and 6). The significance of these findings is discussed later on.

FIG. 3

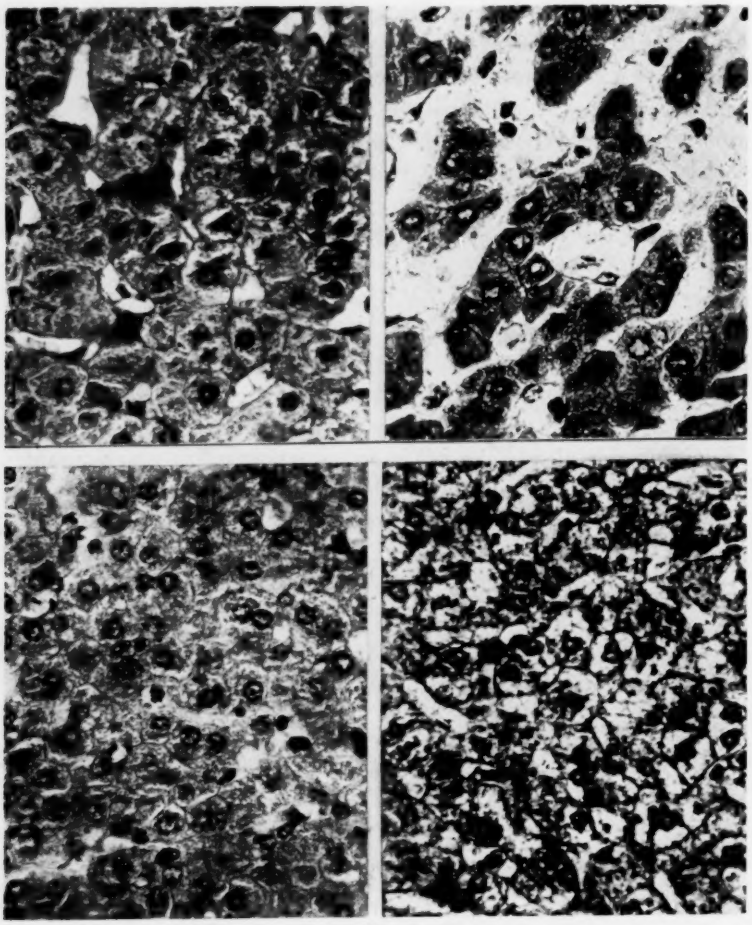


FIG. 4

FIG. 3.—Photomicrographs (× 570) before and after a severe hemorrhage. The patient was a 14-year-old female; a splenectomy carried out. The section at the left shows the condition of the liver as revealed in a biopsy taken at this time. The section at the right is the autopsy specimen removed 6 hours later, death being due to a large intra abdominal hemorrhage. Note the atrophy, the liver cords on the right indicating a depletion of hepatic cytoplasm. The sinusoids are correspondingly dilated.

FIG. 4.—Photomicrographs (× 570) of liver sections obtained at autopsy in fatal experimental hemorrhages in dogs. In the left the bled blood had been replaced by a solution containing hydrolyzed protein, on the right by glucose. Note the loss of stainable hepatic cytoplasm (vacuolization) on the right as compared with the relatively normal liver cords on the left.

COMMENT.—Two features of the present experiments should be emphasized. First, general anesthesia was not used, thus, as pointed out previously,[9] eliminating certain complicating factors in the normal response to hemorrhage. Second, a fatal outcome was invariable in each experiment without altering the details of the procedure, thus avoiding any subjective influence on observations.

The results with serum and plasma replacement have an immediate practical bearing on the use of these fluids in the treatment of human surgical shock. The poor showing of citrated as compared with heparinized plasma is obvious on comparing the blood pressure response as well as the survival time. This confirms experiments performed by others.[3, 14] The fact that citrated plasma produced changes in red cell volume and in plasma proteins which were similar to those with heparinized plasma (Table II) suggests that citrated plasma was just as effective in controlling fluid shifts and colloidal osmotic pressure. It would seem, therefore, that a toxic effect of sodium citrate may have been responsible. That serum was no better than citrated plasma is more difficult to explain, although there is some evidence that serum, under certain conditions at least, is toxic when used instead of plasma.[19] Serum, moreover, behaved unlike plasma in that the changes in hematocrit and plasma protein were somewhat different as indicated by the findings in Table II. For example, the albumin fell more than the globulin, suggesting some loss of this fraction from the circulation. In experiments by others,[14] serum was also found to be inferior to heparinized plasma, in replacement of large single hemorrhages in the dog. Further study of the effect of serum injections seems necessary.

As to the beneficial effects of hydrolyzed protein on survival time and on blood pressure, the most obvious explanation is that they were utilized in the synthesis of serum albumin, thus enabling the body to withstand the effects of further hemorrhages. Study of the hematocrit and plasma protein determinations does seem to justify such an inference. Thus, perusal of Table II shows a slight but definite difference in the behavior of albumin and globulin. It will be noted that the fall in albumin was relatively less (as compared with the globulin) in the experiments in which hydrolyzed protein as compared with those in which glucose was injected. This suggests that more albumin was added to the diluting fluid in the experiments in which hydrolyzed protein was used.

A contrasting result on red cell volume and plasma proteins is apparent in the experiments in which pure amino-acids were used and the ones in which no replacement was carried out. In both of these groups there was very little hemodilution, which means but slight restoration of blood volume. For this reason, the relatively slight fall in protein was of little significance as far as restoration of lost plasma proteins is concerned. Yet the albumin dropped much more than the globulin, indicating loss rather than addition of albumin to the circulating blood during the rather insignificant inflow of fluid. In other words, the compensatory mechanisms controlling fluid shifts seemed less active than in the other experiments. Why the pure amino-acids proved less effective than the hydrolyzed protein is probably due to the fact that they differed significantly in composition from the latter in that they contained no polypeptides and only the essential amino-acids, most of which were synthetic and, therefore, available only as racemic mixtures. Because of the last factor, a majority of the amino-acids were present in the unnatural form, which are probably biologically ineffective.

In evaluating the results with hydrolyzed protein, the biopsy studies of the liver are of considerable interest. In general, they show changes indicating that the liver contained a higher protein content in the experiments with

FIG. 5

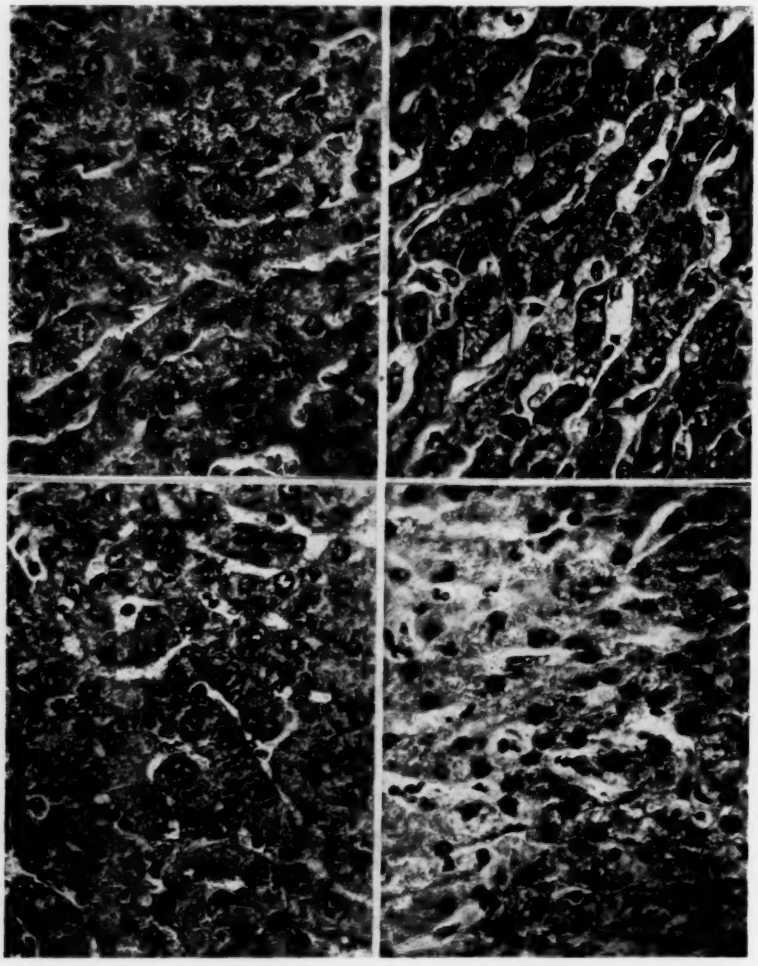


FIG. 6

FIG. 5.—Photomicrographs (× 570) of liver sections before and after repeated hemorrhages; replacement with glucose. This experiment differs from the others in that nembutal anesthesia had to be given to get the control biopsy. Nevertheless note the atrophy of the liver cords as well as vacuolization of the cytoplasm on the right as compared with the control on the left. This change is to be contrasted with Text Fig. 6 in which hydrolyzed protein was used for replacement.

FIG. 6.—Photomicrographs (× 570) of liver sections before and after repeated hemorrhage; replacement with solution containing hydrolyzed protein. Note the relative absence of atrophy and vacuolization on the right as compared with the changes observed in Text Fig. 5.

hydrolyzed protein than in those with glucose (Figs. 5 and 6). This interpretation is based upon many previous studies in which the amount of protein in the liver seemed to be correlated with the stainable protoplasm.[10, 11] Corroborative, are other observations[18] in which stained droplets in the liver,

apparently protein in nature, disappeared following experimental hemorrhage. Moreover, we have observed, in a human, what seems to be a loss of hepatic cytoplasm as a result of a fatal hemorrhage (Fig. 4). Further studies, however, will be necessary before this correlation rests on more secure foundations.

That the speed of the intravenous injection has some influence on the results also seems evident. Thus, many of the experiments described herein were repeated, giving the replacement fluid slowly by intravenous drip over the course of the hour between hemorrhages instead of rapidly following each bleeding. The results were remarkably similar to those reported above, with the exception of glucose and heparinized plasma, which resulted in a slightly longer mean survival time when given slowly intravenously. That the manner of replacement has an important influence was also noted in a report[24] of shock induced in dogs by the tourniquet method; while fatalities were successfully combated by repeated small plasma transfusions, the slow injection of plasma for 30 to 50 minutes following release of the tourniquet resulted in shock and death, although the total amount of plasma given to the two groups was the same. Reasons for this difference were not found on analysis of the data on hematocrit, plasma protein, hemoglobin and blood volume.

A comment should be made in regard to amino-acid mixtures made by hydrolyzing protein, *i.e.*, any protein may be hydrolyzed to any degree. The product used herein was hydrolyzed to about 70 per cent of completion; in other words, 30 per cent of the protein molecule was still in the form of amino-acid aggregates or small polypeptides. The larger these aggregates the more they approach the properties of protein and the more likely they are to possess colloidal properties. These considerations may eventually prove of practical importance, inasmuch, as slightly hydrolyzed proteins may be of sufficient molecular size to exhibit the properties of plasma proteins and yet may have lost any anaphylactic or antigenic properties possessed by the intact molecule. Moreover, no one knows how small the hydrolyzed protein molecule must be before it can be utilized as such by the body in the synthesis of other proteins or for other metabolic needs. Further investigation would seem to be worth while.

Certain additional clinical implications may be drawn from the present data. Hemorrhage, in many instances, will be accompanied by considerable trauma. Whether this be the result of an accident or a planned operative procedure, there is an increased nitrogen loss indicating excessive tissue protein breakdown.[5] When there is acute loss of protein, as in hemorrhage, the body stores will attempt to replenish this loss at their own expense, thus adding to the depletion of tissue protein. To replace protein lost from the circulating blood is a simple problem and can be accomplished directly with whole blood or plasma. On the other hand, correction of tissue protein depletion is easier and more direct with amino-acids than with plasma, even when large amounts of the latter are given. Thus, in the severely wounded or severely depleted individual nitrogen metabolism can be restored to normal more readily by using protein hydrolysates, thus, accelerating recovery. Moreover, if whole

blood or plasma is not available it would seem that protein hydrolysate is preferable to the use of ordinary crystalloid in the treatment of shock due to hemorrhage.

SUMMARY

Fatal surgical shock in unanesthetized dogs followed bleeding ten cubic centimeters per kilo of body weight, every hour, the mean survival time being 3.6 hours. There was a progressive fall in blood pressure, in red cell volume, and in plasma albumin and globulin in all experiments. If the bood removed each time was immediately replaced by the same volume of various solutions, significant differences were observed as follows:

The survival time was unchanged with glucose in saline, increased to 4.2 hours with pure amino-acids, to 5.15 with hydrolyzed protein. With citrated plasma or serum survival time was but 4.5 and 4.6 hours, whereas with heparinized plasma it was 6.0 hours.

The fall in blood pressure was greater with citrated plasma and serum than with heparinized plasma, whereas, hydrolyzed protein produced less hypotension than glucose.

Study of the changes in red cell volume and in plasma proteins gives some indication that the amino-acids of hydrolyzed protein were converted into plasma albumin. Histologic study of the liver suggests that protein is lost from the hepatic cytoplasm in hemorrhage, and that injecting hydrolyzed protein replenishes this loss, as compared with experiments in which glucose was used.

It may be inferred that in shock due to repeated hemorrhage a solution containing the amino-acids and peptides of hydrolyzed protein has a beneficial influence as compared with glucose and that heparinized is far superior to citrated plasma. Various implications of the problem of shock from repeated hemorrhage are discussed.

BIBLIOGRAPHY

[1] Blalock, A.: Principles of Surgical Care. C. V. Mosby, St. Louis, 1940.
[2] Bale, W. F.: (Personal communication).
[3] Bruneau, J., and Graham, E. A.: Arch. Surg. (In press).
[4] Campbell, W. R., and Hanna, M. I., Jr.: Biol. Chem., **119**, 15, 1937.
[5] Cuthbertson, D. P.: Lancet, **1**, 433, 1942.
[6] Davis, H. A., *et al.*: Proc., **37**, 144, 1937.
[7] Domeshek, W., and Loman, J.: Am. Jr. Phys., **101**, 140, 1932.
[8] Elman, R. Annals of Surgery, **112**, 594, 1940; *ibid:* **115**, 1160, 1942.
[9] Elman, R., Lischer, C. E., and Davey, H. W.: Am. Jr. Physiol., **138**, 569, 1943.
[10] Elman, R., Smith, M. R., and Sachar, L. A.: Gastro-enterology, **1**, 24, 1943.
[11] Elman, R., and Weiner, D. O.: J. A. M. A., **112**, 796, 1939.
[12] Elman, R., and Lischer, C. E.: J. A. M. A., **121**, 498, 1943.
[13] Harkins, H. N.: Surgery, **9**, 231–294, 1941; *ibid:* 447–482; 607–655, 1941.
[14] Ivy, A. C., *et al.*: S. G. O., **76**, 85, 1943.
[15] Kendrick, D. B., Jr.: Surgery, **6**, 520, 1939.
[16] Kendrick, D. B., Jr., and Wakins, K. G.: Proc. Soc. Exp. Biol. & Med., **40**, 114, 1939.
[17] Lehman, E. P., and Arnole, C. V.: Surgery, **4**, 44, 1938.

[18] Li, H. M.: Chinese Jour. Phys., **10**, 7, 1936.
[19] Mudd, S., and Thalheimer, Wm.: Blood Substitutes and Blood Transfusions, C. C. Thomas, 1942. Page 112.
[20] Parsons, E., and Phemister, D. B.: S. G. O., **51**, 196, 1930.
[21] Rose, W. C.: Science, **86**, 298, 1937.
[22] Shonheimer, R.: The Dynamic State of Body Constituents. Harvard Univ. Press, 1942.
[23] Sobel, A. E., Yuska, H., and Cohn, J.: Jour. Biol. Chem., **118**, 443, 1937.
[24] Swingle, W. W., *et al:* Am. Jour. Phys., **138**, 156, 1942.
[25] Wiggers, C. J.: Phys. Rev., **22**, 74, 1942.

DISCUSSION.—Dr. Robert Elman (St. Louis, Mo.): The general phenomenon of plasma protein regeneration, particularly by dietary means, has, of course, been extensively studied, especially by the Rochester School, under Doctors George Whipple and S. C. Madden. What we have shown, I believe, is that this regeneration occurs rapidly enough after repeated acute blood loss to have a beneficial effect, provided a proper mixture of amino-acids is injected. Such solutions may, therefore, have a place in the treatment of shock, insofar, as they can be transformed into plasma proteins, thus enabling the body to withstand further loss of blood, which might otherwise prove fatal. This may at least spare the need for much of the plasma which would be required after the initial hemorrhage.

I would like to pursue the biochemical point of view a little further. It seems clear that much of the problem in the treatment of shock following hemorrhage concerns the need for rapid restoration of plasma proteins lost in the bleeding. Now plenty of fluid is available in the body to restore blood volume spontaneously; actually about 20 liters are normally present in the extracellular spaces of an average-sized adult, and it is quickly mobilized after hemorrhage. Unfortunately, however, this fluid contains practically no protein and this is the reason why its compensatory effect is inadequate. True enough, plasma proteins are regenerated eventually, but without outside aid, this requires days instead of hours. Now, if a soldier dies after a total loss of two liters of blood, one could explain the fatality by saying that the patient urgently needed 60 gm. of plasma protein; and that the inability of the body to supply it may be described by a well known phrase—"too little and too late." Yet, consider how strange this is: Sixty gm. of protein needed in the blood stream, while kilograms of tissue protein are present everywhere, without being used. Well might one quote the words of the Ancient Mariner: "Water, water everywhere, nor any drop to drink." According to this line of reasoning experimental studies aiming to find means to supplement or supplant the use of plasma might well be directed toward the possibility of accelerating endogenous plasma protein replacement. Indeed, it may not be too farfetched to look forward to such acceleration from the tremendous tissue protein stores by merely injecting appropriate enzymes or catalysts.

DR. LESTER R. DRAGSTEDT (Chicago): This paper by Doctors Elman and Lischer presents a number of interesting and puzzling facts. I should have anticipated that a single massive hemorrhage would be more apt to be fatal than the gradual loss of the same amount of blood because of the time for the compensatory mechanism to become active in the former case. I should like to know if the authors have any explanation for this contrary finding.

The better results from the use of protein hydrolysates as compared with glucose, it seems to me is very likely to be explained as they have suggested, by the formation of plasma proteins from the amino-acids supplied. It means a much more rapid manufacture of proteins from amino-acids than I would have believed possible.

I wonder if a possible explanation could be that in the presence of this massive hemorrhage protein reserves have been called out from the tissues and that the amino-acids supplied have furnished material for the more gradual replenishment of the tissue proteins.

The superiority of heparinized plasma as compared with citrated plasma I think is of great and practical importance, now that large transfusions are being administered. It seems likely to me that it can be explained on the basis of the toxicity of citrate.

In a recent experience in our clinic, a very large amount of citrated blood was given a patient upon whom I had performed a total colectomy for chronic ulcerative colitis. The patient was a young man. He died on the fifth postoperative day from a cerebral thrombosis. No studies were made of the coagulability of the blood in this patient, but I have since speculated on the possibility that the large amount of citrate given may have increased the coagulability of the blood to a dangerous degree.

This paradoxical effect of citrate *in vivo* was noted by the early workers on blood transfusion, and I believe they called attention to its possible danger.

I should like to ask the authors if they observed any evidence of intravascular coagulation when they gave these large amounts of citrated plasma?

DR. CHARLES C. LUND (Boston): This strikes me as a very important piece of work, and I agree with Dr. Dragstedt that the findings are not exactly what one would have predicted, particularly in this matter of repeated hemorrhage being more serious than the single hemorrhage.

My experience with amino-acid therapy is very recent and is connected with burns rather than with hemorrhage.

If the action of amino-acids in helping to regenerate tissue—that is, regenerate plasma protein—is as rapid as is shown here, which means a matter of hours rather than of days, it may be possible to replace some of the large amounts of human plasma that are used in treating burns by amino-acids. That will be a very important thing in many ways.

In a hospital such as the Boston City, and others that I know about, that have fair numbers of patients coming in with burns, the burn cases are the ones that tend to keep or to produce insolvency in blood banks. Many burn patients, of course, in spite of large amounts of plasma die. Many burn patients have few or no friends, and it is not at all unusual to use up ten or fifteen or twenty units of plasma on a burn case and not have any of them returned to the bank.

Of course, Dr. Elman's experiment has not been carried over from hemorrhage shock into burn shock, but it would seem logical that it might work in burn shock, and would solve this and probably a great many other problems connected with the treatment of burns, shock, and hemorrhage, perhaps in a fairly short time. Although at present the supply of available injectable amino-acids is so short that it is more difficult to get hold of them than it is to obtain plasma, the time may come when we will not have to bleed quite so many million people for plasma supplies, by using amino-acids produced in factories from milk or, as time goes on, other sources of protein.

DR. CARL E. LISCHER (St. Louis, closing): The answer to Dr. Dragstedt's question, as to why the repeated hemorrhage of the same amount is more fatal than a single hemorrhage, we do not know, although it seems to us at times that possibly the repeated injury to the vasomotor system is a factor. After a single hemorrhage the organism is allowed to recover without any further interference, if he does recover, but when you bleed the dog repeatedly, although the total amount is the same, each time he gets into the recovery phase you hit him again. I do not know whether that has anything to do with it or not, but it might.

As far as the difference in clotting in these dogs, there was a vast difference between the dogs that received citrated plasma and those that received heparinized plasma. With those receiving heparnized plasma, it was like turning on a water spigot. With those receiving citrated plasma, after two or three hemorrhages it became difficult at times to get the blood to flow freely, and frequently there were clots and the cannula had to be removed and cleaned before the hemorrhage could be obtained.

In regard to the tissue regeneration or the regeneration of proteins, there has been some work indicating that the amount of protein, for example, in the liver, can be correlated with the stainable cytoplasm. This is more of an idea than an established

fact, because it requires more study, and it is a study in itself, but the liver sections of the dogs that received the protein hydrolysates were, on the whole, better than those getting glucose, as far as stainable cytoplasm is concerned.

Doctor Lund brought up an interesting point in relation to burns. We have tried amino-acids in burn shock in dogs, without any immediate benefit apparently, but we do feel that if the original or initial shock in burns is controlled by replacement therapy with plasma, that the amino-acids are at the present time, even without further work, very valuable in helping to return that patient to a state of normal metabolism during the convalescence and, thus, will greatly accelerate the convalescence while he is losing so much nitrogen, for so many days, following a burn.

TRAUMATIC SHOCK*

AN EXPERIMENTAL STUDY INCLUDING EVIDENCE AGAINST THE CAPILLARY LEAKAGE HYPOTHESIS

JACOB FINE, M.D., ARNOLD M. SELIGMAN, M.D., AND HOWARD A. FRANK, M.D.

BOSTON, MASS.

FROM THE SURGICAL RESEARCH DEPARTMENT, BETH ISRAEL HOSPITAL, AND THE DEPARTMENT OF SURGERY HARVARD MEDICAL SCHOOL, BOSTON, MASS.

TRAUMATIC SHOCK is a state of vascular collapse which develops under such a wide variety of circumstances that some observers regard this condition as divisible into various types according to the etiologic agent involved. Thus, some of the clinical manifestations of burn shock are not seen in the shock of coronary thrombosis or of overwhelming infection. There is, indeed, some discrepancy in the objective findings in the blood chemistry, the hemodynamics, the intra- *versus* extravascular fluid and electrolyte balance, and in the therapeutic response to drugs and fluids. Moreover, there is no unanimity even in respect to the morbid anatomy of traumatic shock, for while one observer adduces evidence of wet or hemorrhagic tissues, another will describe a dry, ischemic state of the tissues.

It is, nevertheless, possible to find common agreement on certain basic issues. When traumatic shock, regardless of cause, exists, it is now agreed that (1) the cardiac output is greatly diminished; (2) the velocity of flow through the peripheral vascular bed is reduced; (3) acid metabolites are present in increased concentration in the blood; (4) the blood carbon dioxide concentration is usually diminished; (5) the venous oxygen concentration is much reduced, while the arterial oxygen concentration may be normal or slightly reduced; (6) the volume of venous return to the heart is reduced; and (7) the blood pressure eventually falls. These phenomena are all invariably present in any and all types, if there are types, of traumatic shock. The focal point of the functional disturbance is in the peripheral vascular bed. It is, therefore, not surprising that urine excretion is diminished, that oxygen consumption is lowered, that the body surface is ischemic and shows evidence of sympathetic nerve dominance.

The foregoing phenomena are inevitable consequences of a critically depleted plasma volume. That such a deficiency exists in most cases of shock is certain. But it has also been shown that shock can exist in the absence of a demonstrable deficiency of plasma volume. There is, therefore, justification for assuming that plasma volume deficiency is not the sole etiology of secondary shock, and that in certain circumstances, to which we shall return later, additional blood or plasma is not the essential need. In the more

* Read before the American Surgical Association, Cincinnati, Ohio, May 13–14, 1943.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

common conditions, where a deficiency may be assumed to exist, the adequate and early replacement of the plasma deficiency will restore the organism, but not if the shock state *has persisted for some time,* even in such a relatively simple situation as shock following hemorrhage. The popular explanation for this failure is that the replaced blood or plasma fails to remain in the blood stream, owing to damage to the capillary walls.

Direct evidence for the existence of capillary damage outside of areas of injury is meager and unconvincing. Capillary damage is seen in the hemorrhagic intestine, in the petechial hemorrhages in the lung and brain or burn shock,[1] and in the adrenal cortex in a variety of conditions culminating in shock. These changes are not seen in all types of shock, nor do they signify the existence of a generalized increase in capillary permeability. Nevertheless, since a large plasma loss may occur through capillaries, which seem intact microscopically, and since such a plasma loss, if uniformly distributed, may exist without producing overtly wet tissues, it becomes necessary to determine the validity of the capillary leakage hypothesis by less equivocal technic than have been utilized heretofore.

This report deals, among other things, with a study of the capillary leakage hypothesis in shock by a technic involving the use of radioactively-tagged plasma proteins.* We shall present evidence (1) invalidating the theory of leakage due to a generalized increase in capillary permeability; and (2) other data which indicate that the peripheral vascular collapse is a state of progressively increasing stagnation of the blood in the capillary bed leading to deterioration of tissue function.

CAPILLARY LEAKAGE IN HEMORRHAGIC, TOURNIQUET AND BURN SHOCK

METHOD: By tagging the plasma protein molecule with a radioactive element, and introducing such plasma protein into the blood stream, an unmistakable label is provided by which to identify the movement of plasma proteins. In order to obtain as physiological a preparation as possible, radioactive cystine was synthesized from radioactive sulfur (80-day half-

* The capillary leakage hypothesis assumes that plasma (or some of its constituents) escapes from the general capillary bed at a greater than normal rate and that it fails to return to the circulation as fast as it leaves, resulting in a net gain of plasma to tissues outside of localized areas of injury. Since the net loss of the non-protein fraction of plasma without a simultaneous net loss of some protein from the circulation will not produce shock (except in the case of shock from extreme and rapid dehydration), a determination of the presence or absence of a net gain of plasma protein to the extravascular portion of the tissues outside of areas of injury should decide whether or not this hypothesis is tenable. (See further discussion under section on Burn Shock). In the subsequent discussion, therefore, while the data obtained refers only to protein shifts, we shall not distinguish between plasma protein loss and whole plasma loss when referring to the concept of leakage due to a generalized increase in capillary permeability. For the purpose at hand, it is not so necessary to demonstrate the existence of an increase in capillary permeability as it is to observe the consequences of such an increase.

life) and fed to plasma protein-deficient dogs, which incorporated the cystine into their own plasma proteins. Plasma protein removed from these dogs was then administered to normal dogs and to dogs shocked by hemorrhage, and its rate of escape from the circulation determined. The number of experiments possible was limited by the scarcity of radioactive sulfur and by the very considerable problem involved in obtaining an adequate amount of radiosulf-plasma protein.[2, 3, 4] As a substitute for the latter, radioactive bromine (34-hour half-life) or iodine (8-day half-life), coupled directly with plasma protein, was utilized. Although radioiodoprotein and radiobromoprotein, so prepared, is denatured, the amount of iodine or bromine incorporated into the protein molecule was minimal and provided a tagged substance whose disappearance rate from the blood in normal dogs was close enough to that of radiosulfprotein to justify its use as a reliable modality for the problem at hand.[5, 6]

In addition to curves of disappearance from the circulation of radioiodo- and bromoprotein, the tissue content of radioactive protein was determined simultaneously. This is necessary because it is not possible to calculate whole plasma loss from blood disappearance curve unless the plasma volume is known with certainty. Since all methods of measuring plasma volume, which depend on dilution of a dye or tagged substance, measure only circulating plasma, reliable calculations of plasma loss are not possible by such technics under all circumstances, especially during the shock state. The direct determination of the protein which has actually left the circulation, by analysis of the tissue content of radioactive protein, constitutes a method independent of plasma volume measurements. This method also provides a means of determining whether or not a preferential leakage into certain areas occurs.

The radioactivity due to intravascular radioactive plasma protein was subtracted from the total tissue radioactivity in order to calculate the extravascular plasma protein. The intravascular plasma content of tissues (and its radioactivity) was calculated from the red cell content of each tissue, as determined by hemoglobin measurements (see below) and the estimated[5, 6, 7] capillary hematocrit. Whenever possible, dogs were exsanguinated at the end of the experiment to reduce the intravascular content of blood in the tissues to a minimum.

In each experiment an unshocked dog served as the control and the dose of radioactive protein injected was generally in proportion to body weight. The amount of protein injected was never sufficient to alter plasma volume significantly. The time from injection to the end of the experiment was the same in both control and shocked dogs. The latter received the radioactive protein before or after shock was induced. Graded hemorrhage, a burn, or a tourniquet[8] was used to produce shock. Except for five early experiments under intravenous sodium barbital, no anesthesia, except novocain for local incisions, was used, but morphine was given to all dogs

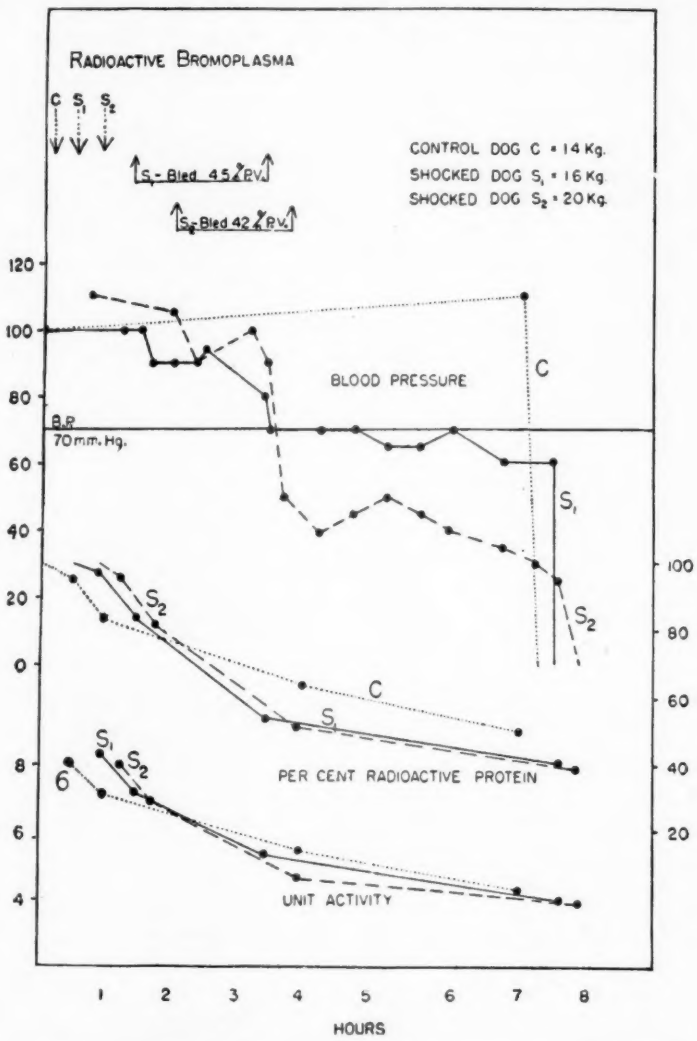


FIG. 1.—*Experiment B—11:* The increased slope of both radioactivity curves for Dogs S_1 and S_2 as compared to that of Dog C, immediately after bleeding, is probably due to dilution by mobilized extravascular fluid. Their subsequent parallel course indicates that the shocked dogs did not lose radioactive protein from the plasma at a greater rate than the control dog. There is no difference in the disappearance curves between the dog in deep shock (S_2, probably irreversible) and the dog in less severe shock (S_1, probably reversible). (Reproduced with the permission of the Journal of Clinical Investigation).

at the beginning of each experiment. The burns were produced under ether by immersion in water at 98° C. for varying periods.

No therapy for shock was given, except in the late shock phase of some experiments, when intravenous fluids were injected to see whether an increase in capillary permeability, which may have developed during this phase, could be made manifest by flooding the circulation with a sufficiency of fluids to allow excessive leakage, if this were possible.

Some fourteen experiments were performed, most of which included tissue analyses for lost plasma protein. The full account of the technics and calculations involved in these procedures is published elsewhere.[5, 6]

RESULTS

A. HEMORRHAGIC SHOCK

The detailed results of seven experiments with radiobromoprotein will not be analyzed here since they are available in a recent publication.[5] It will be sufficient to reproduce our experience in a typical experiment.

Exper. No. B-11: Three morphinized dogs, C (control), S_1 (to be bled into reversible shock), and S_2 (to be bled into irreversible shock), were given radioactive plasma protein intravenously in protein to their body weight. Dogs S_1 and S_2 were then bled into shock. The blood pressure was followed and blood samples were taken at varying intervals until Dog S_2 died. At this time Dogs C and S_1 were exsanguinated and samples of different tissues (Table I) from all three dogs were taken for analysis of

TABLE I

RATIO OF TISSUE RADIOACTIVITY OF SHOCKED DOGS TO COTNROL DOG*

Experiment B—11

Tissue	Dog S_1 Per Cent	Dog S_2 Per Cent
Liver	59	99
Lung	110	91
Kidney	185	125
Stomach	67	83
Ileum	66	68
Colon	67	56
Skin (thorax)	215	235
Skin (back)	130	110
Heart	130	135
Muscle (foreleg)	110	88
Muscle (spinal)	89	88

* A ratio of 100 per cent indicates equal radioactivity per gram of tissue in control and shocked dogs. Less or more than 100 per cent signifies a lower or higher radioactivity per gram of tissue in the shocked dog.

Ratios varying between 75 and 125 per cent are considered within the limits of experimental error in the experiments with radiobromoprotein. See footnote on page 244.

intravascular and extravascular radiobromoprotein content. The disappearance of radioactive bromoprotein from the blood is charted in Figure 1 in terms of (a) radioactivity per cubic centimeter of circulating plasma, and (b) total circulating radioactivity in per cent of the original amount injected. The latter is calculated as the product of the determined plasma volume and the unit radioactivity. The slope of both curves for Dogs S_1 and S_2 immediately after bleeding shows an increase as compared to Dog C, probably due to dilution by mobilization of extravascular fluid.[9] But the subsequent parallel course of all three curves indicates (1) that the dog in deep shock did not lose radioactive protein from the circulating blood plasma at a

greater rate than the control dog; and (2) that the dog in deep shock did not lose radioactive protein faster than the dog in moderate shock.

Analysis of the tissues of the three dogs showed further that the extravascular plasma protein content of all tissues, except kidney and skin of thorax, did not differ substantially from one another (Table I). The calculated protein and plasma loss into kidney and skin of thorax was, furthermore, not significant quantitatively.

With certain minor variations similar results were obtained in most of the comparable experiments performed with radiobromoprotein.

The foregoing experiments provided no evidence of greater leakage of protein in irreversible shock than in reversible shock. An increase in capillary permeability to protein that may have developed in the former might have been elicited if the stagnant or collapsed capillaries had been supplied with a sufficient volume of fluid to force fluid transfer. Accordingly, experiments were carried out in which a transfusion was given to two shocked dogs when one had become irreversible. The following is a representative example:

Exper. I-7: The two dogs (Nos. 98 and 99) were bled into shock by hemorrhage. After seven and one-half hours in shock, when the blood pressure was 20 mm. Hg., Dog 98 was given a transfusion of 470 cc. of plasma containing radioiodoprotein. At the same time a transfusion of 345 cc. of plasma containing radioiodoprotein was given to Dog 99, which had been in shock for three hours, when the blood pressure was 30 mm. Hg. Dog 98 did not recover and when the blood pressure again declined to 25 mm. Hg. the blood pressure of Dog 99, which was recovering, was 100 mm. Hg. Both dogs were exsanguinated simultaneously, Dog 98 yielding 70 cc. and Dog 99 230 cc. of blood. Tissue samples for analysis were taken immediately from both, with results shown in Table II, in which the ratio of radioactivity content per gram of tissue of Dog 98 to that of Dog 99 is given.

TABLE II

RATIO OF RADIOACTIVITY (RADIOIODOPROTEIN) OF TISSUES OF DOG IN IRREVERSIBLE HEMORRHAGIC SHOCK AS COMPARED TO CONTROL DOG IN REVERSIBLE HEMORRHAGIC SHOCK, INCLUDING PLASMA LOSS IN WHOLE ORGANS IN SHOCKED (IRREVERSIBLE) AS COMPARED TO CONTROL (REVERSIBLE SHOCK) DOG*

Experiment I—7

Tissue	Ratio Per Cent	Plasma Loss Cc.
Liver	13	0
Lung	32	0
Kidney	87	0
Intestine	68	0
Spleen	112	1
Skin	41	0
Heart	62	0
Muscle	121	9.5
Total	..	10.5

* Ratios varying between 95 and 105 per cent are considered within the limits of experimental error in the experiments with radioiodoprotein.

Except for muscle and spleen, all the tissues of Dog 98 contained less extravascular plasma than those of Dog 99. There is, accordingly, no evidence of greater leakage of plasma in the dog in irreversible hemorrhagic shock as compared to the dog in reversible shock. On the contrary, the former, probably because of a less efficient capillary circulation, seems to have displayed a slower than normal rate of escape of iodoprotein from the circulation.

Since the forces operating to produce lethal shock are not necessarily the same in all types of shock, it became necessary to obtain data on the question of generalized increase in capillary permeability in conditions other than hemorrhage. Tourniquet shock and burn shock were studied by the above described technic, using radioiodoplasma protein, which turned out to be the most advantageous preparation of the three types of radioactive plasma utilized in this study. Tourniquet shock and burn shock differ from hemorrhagic shock in that (1) a local loss into areas of injury occurs; and (2) such injured tissues perhaps may liberate a substance capable of affecting capillary permeability in general.

B. TOURNIQUET SHOCK

A tourniquet was applied at the groin to one or both legs of a dog under morphine (3 mg. per Kg.) and left on for some seven hours. Plasma volume was then measured and radioiodoprotein was given to this dog and to a normal morphinized dog in equivalent amounts. The tourniquet was removed and the same measurements as in Experiment I-7 made. The detailed data is available elsewhere.[6] Table III lists the tissue analyses of four dogs (I-2 A, I-2 B, I-3 and I-4) showing plasma protein loss in various tissues including the tourniqueted extremities. While the ratio* of the radioactivity content of the shocked dog's tissues to that of the control dog's tissues indicates loss of protein into some tissues other than the ex-

* When radioiodoprotein is used, any ratio below 95 or above 105, except in muscle, is taken to represent a difference outside of experimental error. This error is much smaller than in the case of radiobromoprotein.[5] The significance of such ratios is not evident in the ratio figures themselves since two factors of importance affect the calculation. These are the relative weights of the organ and the relative radioactivity measurements of such organs per gram. For example, if a ratio of 200, derived from a radioactivity of .001 div. per sec. on the electroscope in the control and a radioactivity of .002 div. per sec. in the shocked dog, applies to a gram of tissue of a given organ (A); and the same ratio, derived from a radio-activity of .0001 div. per sec. in the control and .0002 div. per sec. in the shocked dog, applies to a gram of tissue of another organ (B) of the same weight, the difference in radioactivity per gram of tissue will be .001 for organ A and .0001 for organ B. The total radioactive protein content of organ A will be ten times that of organ B and the quantitative loss involved is obviously far less in organ B, even though the ratio is the same for both. The relative activities of various tissues in normal dogs are shown in another publication.[5] The quantitative significance of an increased ratio is of little consequence in an organ like the kidney, which is small in weight, and the same is true when a large organ has a very low order of radioactivity.

tremities, such loss involves only one to three tissues and in no case is the total loss outside of the extremities quantitatively significant, from the point of view of plasma protein depletion. There is, therefore, no evidence that a change in permeability to proteins, outside the area of injury, if it exists, is of consequence in the development and progression of shock following the removal of a tourniquet.

The volumes of plasma lost into the tourniqueted extremities is of course large. The gain in weight was not determinable in Experiments I-2 A and I-2 B, where both legs were injured, but in Experiments I-3 and I-4 the weight increase (above the opposite normal leg) was much greater than the plasma gain determined by radioactivity assay of the tissues (Table IV). This discrepancy is far in excess of errors in method. The difference, therefore, in major part, represents a gain in tissue water drawn from outside areas.

The plasma gain in the leg in three of the four shocked dogs listed in Table III is less than the plasma loss found by circulating plasma volume determinations (Table IV). It was pointed out elsewhere[5] that in deep shock plasma volume measurements by the dye technic may overestimate loss because the segregation of more plasma into the stagnant peripheral bed as shock deepens (a progressive rise in the amount of trapped plasma) will increase the extent of incomplete mixing and so give too low a dye dilution figure in terms of the total plasma volume. Hence one may expect a discrepancy between the dye method and the tissue radioactivity method, the former showing a falsely higher loss, the more stagnant the peripheral bed becomes. But the much greater total fluid loss into the leg, found by actual weight change, than is disclosed by the dye method again points to a large access of tissue water derived from extravascular sources.

C. BURN SHOCK

Three experiments were performed in which one or more extremities were immersed under ether anesthesia for varying intervals in water at 98° C. (Tables III and IV). In Experiments I-5 and I-6 radioiodoprotein was injected intravenously into a normal dog and into the burned dog before the burn was produced. In Experiment I-8 the technic was varied in order to see whether the capillaries were more permeable to protein in a severely burned than in a mildly burned animal. For this purpose two dogs were burned, one for 120 seconds, the other for 20 seconds. Four hours before death of the more severely burned dog a plasma infusion containing radioiodoprotein was given simultaneously to both dogs.

The extravascular radioactive protein content of the tissues in all three experiments showed no significant difference in the plasma protein content of the unburned tissues of the burned dog in comparison with the same tissues in the unburned control dog (Exper. I-5 and I-6) or the less severely burned control dog (Exper. I-8).

TABLE III

RATIO OF RADIOACTIVITY (RADIOIODOPROTEIN) OF TISSUES OF DOGS IN TOURNIQUET OR BURN SHOCK AS COMPARED TO CONTROL DOGS, INCLUDING PLASMA LOSS IN WHOLE ORGANS IN SHOCK AS COMPARED TO CONTROL DOGS

	Tourniquet Shock								Burn Shock					
Exper. No.	I—2A		I—2B		I—3		I—4		I—5		I—6		I—8*	
	Ratio Per Cent	Plasma Loss—Cc.	Ratio Per Cent	Plasma Loss—Cc.	Ratio Per Cent	Plasma Loss—Cc.	Ratio Per Cent	Plasma Loss—Cc.	Ratio Per Cent	Plasma Loss—Cc.	Ratio Per Cent	Plasma Loss—Cc.	Ratio Per Cent	Plasma Loss—Cc.
Liver	97	0	0†	0	118	2.6	64	0	0	0	53	0	140	15
Lung	100	0	0	0	230	7.0	120	2.0	0	0	70	0	147	9
Kidney	176	1.3	0	0	109	0.7	95	0	130	2.1	47	0	0	0
Intestine	222	33	15	0	96	0	52	0	155	20	17	0	57	0
Spleen	170	2.0	0	0	132	0.4	155	1.4	140	0.7	90	0	0	0
Skin	0	3.6	185	3.5	86	0	66	0	23	0	150	5	114	3
Heart	75	0	104	0.4	95	0	67	0	100	0	75	0	94	0
Muscle	76	0	0	43	138	7.0	104	3.5	57	0	120	7	116	10
Injured extremities	400	102	0	132	2800	122	950	180	310	190‡	2200	445‡	300	24§
Totals	..	143	..	179	..	140	..	184	..	213	..	457	..	61

* The control dog in this experiment was also burned, one more severely than the other to compare severe and mild burn shock states.

† Where no radioactivity is found in the extravascular tissue of the shocked dog, the ratio becomes zero.

‡ If loss of plasma is assumed to have occurred early after the burn, these values would be halved.

§ Plasma loss into the burned legs was calculated by comparison with values for intact muscle and skin for both dogs. Plasma loss in milder burn was 38 cc. Small loss was due to the fact that leakage occurred before radioiodoprotein was given (four and one-half hours before the end of the experiment).

TABLE IV

PROTOCOL DATA IN TOURNIQUET SHOCK AND BURN SHOCK AND COMPARISON OF PLASMA LOSS INTO INJURED EXTREMITY BY THREE CRITERIA

Type of Shock	Exper. No.	Dog No.	Dog Wt.	$\frac{Ws}{Wc} \times \frac{Ic^*}{Is}$	Duration of Tourniquet (hours) or Burn (seconds)	Duration of Exper. after Removal of Tourniquet or Burn	Blood Pressure at End of Exper.	Volume of Exsanguination at End of Exper.	Hematocrit Increase	Decrease in P.V. by Dye Method†	Wt. Increase of Injured Extremity	Plasma Loss into Injured Extremity by Radioactivity Analysis of Tissue†	Remarks
			Kg.			Hours	Mm. Hg.	Cc.	Per Cent	Cc.	Gm.	Cc.	
Tourniquet	I—2A	84	8.7	1.0	5	5.7	75	270	8	300	..	102	Tourniquet on both hindlegs.
		85	6.9		control	..	110	160	0	...	..	...	
	I—2B	86	10.6	0.93	8	4.0	0	0	13	307	..	132	Tourniquet on both hindlegs.
		87	5.1		control	..	110	200	0	...	..	...	
	I—3	88	11.8	0.92	10.5	5.7	10	30	16	257	360	122	
		89	14.1		control	..	120	500	0	...	...	...	
	I—4	90	13.4	1.0	7.5	11.5	30	100	4	220	435	180	After 7 hours the increase in hematocrit was 13% (Dog 90).
		92	8.2		control	..	105	150	0	..	..	..	
	I—5	94	8.5	0.98	45	27	0	0	1	45	121	190	Burn of foreleg and hindleg. B.P. remained at 80 Mm. Hg. and dropped to 30 Mm.Hg. after a small dose of nembutal (Dog. 94).
		95	5.0		control	..	110	200	0	..	..	..	
Burn	I—6	96	11.6	1.0	90	18.5	0	0	16	230	..	445	Burn of both hindlegs.
		97	10.6		control	..	110	480	2	...	...	...	
	I—8	200	11.8	1.0	120	22	30	0	8	785	69	24§	Plasma infusion (325 cc.) with radioprotein.
		201	10.1		20	21	95	150	11	250	171	38§	Plasma infusion (270 cc.) with radioprotein.

* Formula showing relative proportion of radioiodoprotein dosage to weight of shocked versus control dog, when W = wt. of dog, I = volume of radioactive plasma injected, c = control dog and s = shocked dog.

† In burn experiments plasma volumes by due method were complicated by marked hemolysis.

‡ Data from Table III.

§ Since tagged infusion was given four and one-half hours before end of experiment, loss during this period only was determined.

In Experiment I-5 and I-6 there is no correspondence between the plasma volume loss into the burned extremity, as estimated from radioactive plasma protein content, and the loss as measured by intravenous dye. The unavoidable hemolysis of blood in burned dogs affects the reliability of the latter method.

In Experiment I-8 the radioactive protein content was injected too late to permit a determination of total protein loss into the burned area. In the severely burned dog the very small increase in weight of the burned extremity suggests that peripheral vascular collapse was due to factors other than plasma volume deficiency.

Although the extent of the plasma volume loss into the tissues in the foregoing experiments cannot be assessed with complete accuracy, the loss outside of areas of injury involves only one or two tissues, which vary from one experiment to another, and, in any case, is not quantitatively significant.

The calculation of plasma volume loss into tissue is based on the assumption that if such loss occurs outside of areas of local injury, whole plasma is lost. If greater capillary permeability to the nonprotein than to the protein fraction of the plasma should exist, the disproportion between the loss of the protein and the nonprotein fraction of plasma would be reflected in a shift of the total protein concentration. Since the latter does not increase in hemorrhagic shock,[10] plasma if lost would be in proportion to protein loss in hemorrhagic shock, except perhaps when saline infusions are given in the late shock phase. The rise in total protein concentration in burn shock and in tourniquet shock may be explained as due to a disproportionate loss of the nonprotein fraction into or outside the injured area. Such loss, if substantial, into tissues outside the injured area would not be likely without a loss of a measurable amount of protein. Since no protein is lost (*i.e.*, no loss of consequence, except in a sporadic and inconsistent manner involving one or two tissues varying from one experiment to another) into areas outside the locally traumatized area in either burn shock or tourniquet shock, our assumption that no plasma is lost outside of areas of local injury seems justified.

Evidence that plasma does not escape from the general capillary bed in untreated shocked dogs appears in plasma volume measurements in 24 dogs in hemorrhagic shock listed in Table V. These showed an average gain of nine per cent above the expected amount, owing to mobilization of extravascular fluid during an early phase of shock. In 12 of these experiments plasma volume was measured again after a subsequent interval of shock. In seven of these no therapy was given and the volume was substantially unchanged. The remaining five received a saline, plasma or blood transfusion in the late shock phase, with an average volume 19 per cent below what was expected from the volume of the infusion added to the previous volume determination. The discrepancy between the expected and determined volume might have been due to loss into tissues (particularly in the case of saline infusion), but it might also have been due to inadequate

TABLE V*

PLASMA VOLUME IN HEMORRHAGIC SHOCK

Exper. No.	Plasma Withdrawn to Produce Shock Per Cent	Plasma Volume in Shock: First Measurement — Duration of Shock Hours	Expected Per Cent	Found Per Cent	Gain or Loss Per Cent	Second Measurement — Duration of Shock Hours	Expected Per Cent	Found Per Cent	Gain or Loss Per Cent	Remarks
1	46	1½	54	76	+22	4½	73	69	−4	
2	46	1	54	67	+13					
3	63	1	37	55	+18					
4	60	1½	40	60	+20	4½	55	57	+2	
5	71	3	29	54	+24					Bleeding continued during shock.
6	35	2	65	46	−19					
7	36	3	64	64	0					
8	45	½	55	63	+8	3	56	56	0	
9	44	2½	56	72	+16					
10	28	3½	72	66	−6	4½	63	66	+3	
11	45	1	55	65	+10					
12	39	10	61	65	+4					
13	34	6	66	64	−2					
14	61	5½	39	75	+36					
15	40	2½	60	81	+21	4	61	65	+4	
16	25	1½	75	96	+21	3	85	85	0	
17	20	1	80	84	+4					
18	42	3	58	78	+20	4¼	71	75	+4	
19	58	4	42	51	+9					
20	36	2½	64	53	−11	5	85	78	−6	2nd reading 1½ hrs. after blood transfusion.
21	42	2½	58	64	+6	7	106	90	−16	2nd reading 3 hrs. after blood transfusion. Recovered.
22	15	1	85	70	−15	2	123	98	−25	2nd reading ¾ hr. after plasma transfusion.
23	42	3½	58	58	0	4	97	87	−10	2nd reading ½ hr. after plasma transfusion.
24	68	2	32	59	+27	2½	119	85	−34	2nd reading ½ hr. after 500 cc. saline infusion.
Average					+9.3					

All dogs died except as noted.

* Reproduced with the permission of the Journal of Clinical Investigation.

mixing of dye with capillary blood since the validity of the dye method for total plasma volume measurement depends on complete mixing of the dye with the peripheral blood. If in the late shock phase the peripheral blood is not in active circulation, in the same sense as the peripheral waters of a swamp, through whose center a brook runs, are not in active circulation, complete mixing may not occur in the time interval allowed (15–30 minutes). The results with respect to plasma loss obtained by the dye volume method may be said not to disagree with those obtained by the radioactive protein technic.

STAGNATION (OR TRAPPING) OF BLOOD IN THE PERIPHERAL CIRCULATORY BED

That stagnation can explain the discrepancy between expected and observed plasma volumes in the late phase of shock may be inferred from a variety of data: (a) The steadily declining venous oxygen concentration; (b) the increasing divergence in plasma p_H values in favor of a relatively greater acidity on the venous side of the circulation; (c) the increasing divergence in the plasma CO_2 values due to the lesser fall in CO_2 concentration on the venous side of the circulation; (d) the obviously slow or even absent flow through much of the peripheral bed in deep shock, as seen by

capillary microscopy in the rat's mesentery[11] and dog's omentum; and (e) the reversal of all these changes in the direction of normal during the transient recovery phase following a large saline infusion.[12]

In collaboration with Gibson and Evans,[7] who will publish the full data elsewhere, we have obtained evidence that the peripheral circulatory bed and its contained blood is, so to speak, out of contact with the central circulation, and that much of the blood in the latter traverses a shortened circuit. It may be sufficient here to refer briefly to the technic utilized and to quote a few representative results:

Morphinized dogs were given an intravenous dose of red cells containing radioactive iron (47-day half-life) and the red cell volume was determined by the same technic as is used for plasma volume by the dye method. The plasma volume was also measured at the same time. Bleeding into shock was then performed, and after some hours in shock an additional dose of radioactive red cells was given. In a number of experiments the resulting increase in radioactivity per cubic centimeter of cells was more than the expected amount. The red cell volume calculated on the basis of these data was less than the expected volume allowing for the volume of red cells removed by bleeding. This is regarded as evidence of stagnation of red cells somewhere in the peripheral bed.

Further evidence of stagnation (or trapping) was obtained as follows: Dogs in hemorrhagic shock received a dose of radioactive red cells. Upon death of the dog the number of red cells in cubic centimeter per gram of tissue was determined by two methods:

$$\text{A.}\quad \frac{\text{Hb. in 1 gram tissue}}{\text{Hb. in 1 cc. arterial blood (just before death)}} \times \text{arterial hematocrit}$$

$$\text{B.}\quad \frac{\text{Radioactivity (Fe*) per gram of tissue}}{\text{Radioactivity (Fe*) 1 cc. arterial blood (just before death)}} \times \text{arterial hematocrit}$$

Formula A is a method of direct determination of the total number of red cells in cubic centimeter per gram of tissue, but formula B is a determination of the true number of red cells in cubic centimeter per gram of tissue in sufficiently active circulation to have reached the tissue from the time of injection until death. The discrepancy between the results of the two formulae is a measure of the incompleteness of the mixing and, therefore, of the extent of trapping of blood out of active circulation. The average ratio of B/A was found to be 1.0 ± 0.1 in nine normal morphinized dogs. The average ratio in the shocked dogs was 0.7 to 0.8, indicating that some 20 to 30 per cent of the red cell volume in tissues was trapped in the peripheral bed, *i.e.*, by-passed by the active stream.

Such a degree of trapping could not be demonstrated with equal uniformity for plasma. Possibly this may be due to a partial balancing of trapped plasma by mobilized extravascular fluid. It may also be that in

shock the mixing of plasma in active circulation with that in the peripheral bed is physically easier than is the case for particulate material such as red cells. The latter hypothesis is thought not to be true for the normal dog according to Hahn, *et al.*[13]

As shock deepens the trapping may be expected to increase. In recent experiments the technic adopted for measuring the volume of trapped blood was altered in order to avoid errors (see below) inherent in hemoglobin measurements for determination of blood content. This was done as follows: A dose of radioactive red cells, containing radioactive iron with a five-year half-life, was injected during the preshock phase and when the dog was in late shock, a dose of radioactive red cells with a 47-day half-life was injected. The latter, insofar as it might fail to mix completely, would show a deficiency in the previously determined total red cell volume due to trapping.

Analyses of the tissues for the two types of radioactive iron was then made. The number of red cells in cubic centimeter per gram of tissue was then calculated on the basis of the content of each type of radioactive iron.* The two determinations would be expected to agree if complete mixing occurred when both types of radioactive red cells were injected. If stagnation were present when the second dose (47-day half-life radioactive iron) was injected, the cubic centimeter of red cells per gram of tissue, calculated on the basis of 47-day half-life radioactive iron, would be less in proportion to the degree of stagnation. This was found to be the case.

On an average, the tissue content of 47-day half-life iron was some four-fifths of that of five-year half-life iron. Dilution of the second dose of radioactive red cells was likewise approximately four-fifths of the expected amount. The ratios by both technics indicate that there was stagnation of some 20 per cent of the red cell volume of tissues.

An even more extensive segregation of blood in the peripheral bed was observed in Exper. I-8 (Table IV), in which a severe burn was inflicted on one hindleg of a dog weighing 11.8 Kg. Twenty-two hours later the dog was in deep shock, but the hindleg gained only 69 grams in weight. The original plasma volume was about 600 cc. and 325 cc. of plasma had been infused. By the dye plasma volume method a subsequent decrease or "loss" of 785 cc. in plasma volume was measured. This value may be too high due to marked hemolysis from the burn. However, since little loss occurred into the leg, as indicated by the small weight gain and a rise of only eight per cent in hematocrit, the loss indicated by the dye volume method was obviously loss out of active circulation, but not loss from the capillary bed.

In burn shock and in other types of trauma plasma is continuously lost because of the leakage *at the site of injury,* but leakage through the general

* Prof. Robley Evans, and coworkers, of the Massachusetts Institute of Technology constructed Geiger counters which are capable of distinguishing between and accurately determining the radioactivity of the two types of iron in the same blood or tissue sample.

capillary bed does not occur. In hemorrhagic shock an initial loss of plasma is produced, but a progressive decline in plasma volume cannot be demonstrated because leakage does not occur through any capillary area. The difference between the hemodynamic disequilibrium in such states of shock in which there is continuing local loss and that of shock due to hemorrhage, in which hemorrhage has stopped, is merely a quantitative rather than a qualitative one. Once a sufficient initial decline in plasma volume occurs in any type a fatal mechanism is in operation and it is, therefore, not necessary to explain death from shock as involving a *progressive* loss in plasma volume.

On the other hand, the foregoing data (on stagnation or trapping) demonstrates that shock is a state in which a progressive decline in *effective circulating plasma volume* exists. *The total plasma volume may be deficient, but this is not always so.* Thus, if shock is precipitated by an initial critical loss of plasma, a deficiency will be present; if shock is precipitated for some other reason, *e.g.*, severe infection or toxemia, a deficiency in plasma may not be present. Ebert and Stead[14] could find no deficiency in the plasma volume of eight patients in shock as a result of severe coccal infection. It is possible that here, as in the case of our hemorrhagic shock experiments (Table V), a deficiency might have been observed in a later phase of shock. But again, such a deficiency could well be explained as due to incomplete mixing with blood which is stagnant in peripheral areas.

Since shock can exist in the absence of a demonstrable fall in plasma volume, or after replacement of a known deficiency, and since the replaced plasma does not leave the circulatory bed, the essential *defects in irreversible shock are* (1) *inefficient circulatory distribution of the total blood volume;* and (2) *inadequate velocity of flow through capillaries, even when the blood volume equals or exceeds that present before shock occurred.*

The vascular tree in shock shows widespread vasoconstriction (though it is not maximal). In hemorrhagic, burn or tourniquet shock the small arteries and veins of the omentum in the dog or of the web of the foot or the mesentery in the rat are narrowed and the capillaries are empty or nearly empty of red cells. Chambers, Zweifach and Lowenstein[11] have observed dilatation of arterioles, capillaries and venules in a rapidly fatal type of tourniquet shock, in which the extent of the fluid loss into the tourniqueted extremity is limted by a quick collapse resulting possibly from a toxic factor. Terminal relaxation of the arteries (but not of the veins) in the mesentery of the cat in tourniquet shock under barbiturate anesthesia was noted by Page and Abell.[15] Whether the dilatation observed by Chambers, *et al.*[11] and the terminal relaxation observed by Page and Abell occurs in the absence of barbiturate remains to be determined.

These observations, suggesting decreased blood content of the peripheral circulatory bed, receive support from direct estimations of the blood content of the tissues in shock. These were made by the following method:

Weighed amounts (two grams) of various tissues of dogs in shock were taken immediately after death from shock, or in normal dogs, following

exsanguination or intravenous nembutal or potassium cyanide. Blood in large vessels or on the surface of tissue samples was gently wiped away so that only blood in the smallest vessels was left in the tissue. Representative pieces of such tissues as lung, liver, bowel, skin and muscle were pooled and aliquots taken for analysis. The tissues were finely minced, extracted with distilled water at 4° C.* for 24 to 36 hours, and filtered through gauze. The hemoglobin in the filtrate was measured after clearing with ammonia in a photo-electric colorimeter against standards from arterial blood (taken at time of death), using a 620- and 540-filter to correct for turbidity. No correction for methemoglobin was made. Although inaccuracies in the hemoglobin measurement are unavoidable, the red cell volume in cubic centimeter per gram of tissue agreed by this method sufficiently in experiments with simultaneous red cell content determinations made by the radioiron red cell technic,† to permit acceptance of our results as a fair

TABLE VI

AVERAGE VOLUME RED CELLS (CC.) PER GRAM OF TISSUE OF VARIOUS ORGANS IN NORMAL AND SHOCKED DOGS HEMOGLOBIN AND RADIOACTIVE IRON DETERMINATIONS

Tissue	Normal* Cc.	Normal Exsanguinated Cc.	Hemorrhagic Shock Cc.	Tourniquet Shock† Cc.	Burn Shock Cc.	Normal† Cc.	Hemorrhagic Shock‡ Cc.
Liver	.050	.011	.054	.037	.043	.058	.021
Lung	.073	.038	.095	.038	.071	.079	.052
Kidney	.055	.019	.035	.036	.054	.047	.024
Intestine	.0092	.0016	.017	.006	.005	.011	.0033
Spleen	.186	.021	.050	.060	.120	.30	.067
Skin	.0022	.00090	.003	.002	.001	.0065	....
Heart	.0094	.0045	.017	.005	.004	.018	.0082
Muscle	.012	.0050	.021	.005	.005	.0062	.000
Injured extremity	....	....	....	.005	.019	....	....
No. of dogs	7	7	8	5	4	5	1

* Killed by intravenous injection of nembutal or cyanide (two dogs).
† Some of the dogs received infusions of blood (2), plasma (3), or saline (1), and (3) were exsanguinated.
‡ Determination by radioactive red cell measurement.

approximation to the facts (Table VI). From the hemoglobin value the red cell content per gram of tissue was calculated from formula A given above. The liver, lung, kidney and spleen are the only organs containing appreciable amounts of red cells per gram. When the number of red cells per gram of tissue in dogs in shock is compared to that of the normal dog, there is seldom more, and usually less, in the shocked dog (Table VI).‡ In general, it appears that the red cell volume is not greater and is probably somewhat less than normal in the peripheral circulatory bed.

However, direct estimations of the blood content of the tissues in shock by hemoglobin measurements do not indicate what fraction of the blood found in the vessels of these tissues was in circulation in shock. Such data can be obtained by radioactive iron measurements in tissues after injection of red cells, tagged with five-year half-life iron before shock and of red cells, tagged with 47-day half-life iron during shock as described above.

* Myoglobin of heart and skeletal muscle was first extracted with saline solution following which the residue after centrifugation was extracted with distilled water.

† In collaboration with Gibson, Evans, *et al.*[7]

‡ The acutely exsanguinated normal dog shows fewer red cells per gram of tissue than the nonexsanguinated normal dog or the dog shocked by hemorrhage.

The capillary bed normally contains some 20 per cent of the total blood volume. In shock this percentage is not only not increased, but probably is decreased. Data obtained with radioactive red cells indicates that some 20 per cent of this capillary blood volume is trapped out of the active circulation. Although this amount of trapped blood is only some four per cent of the total blood volume, it is, nevertheless, a serious threat to normal tissue function since the capillary bed is the "business end" of the circulation. It is perhaps of no great consequence whether the blood content of tissues at any moment is the same, somewhat more, or somewhat less than normal. The important fact is that this blood, whatever its amount, is not moving at a sufficient velocity through a sufficient number of capillaries to maintain normal tissue function.

COMMENT: The extent of the disturbances in tissue function is indirectly indicated by the level of the venous oxygen concentration and the cardiac output. In extreme states of shock the venous oxygen levels are below five volumes per cent, and the cardiac output may be well below 50 per cent of normal. Anuria or oliguria may be due to decreased velocity of flow or to kidney cell injury. Long and Engels[16] report in rats an increase in the blood amino-acid levels due to failure of deamination by the liver as a result of anoxemia of the portal blood vein, the main source of the oxygen supply to the liver. Disturbances in enzymatic function are indicated by the increase in pyruvic and lactic acid blood levels. Alexander,[17] and Lamson[18] find that the thiamin-cocarboxylase mechanism is seriously affected.

The therapeutic problem in shock which has not yielded to adequate plasma volume replacement becomes one of restoring normal velocity of flow through the capillary bed. Capillary and venous anoxemia rise toward normal when the velocity is accelerated.[12] Whether this increase in velocity of flow necessarily involves a simultaneous increase in cardiac output requires further investigation. Pressor amines do not improve velocity of flow or cardiac output in shock.[19] Pure oxygen even at three atmospheres does not significantly improve the peripheral circulation.[12] Other substances which may improve the peripheral circulation in shock are being investigated.

CONCLUSIONS

1. Plasma proteins tagged with radioactive isotopes (S^{35}, Br^{82}, I^{131}) were used to study the capillary leakage hypothesis in hemorrhagic, tourniquet and burn shock. No evidence of leakage due to a change in the permeability of the general capillary bed was found. Tagged plasma proteins escaped into areas of injury in considerable amounts, but not into untraumatized areas.

2. There is no evidence to show that the general capillary bed becomes more permeable to plasma proteins or plasma in the late or irreversible phase of shock.

3. Data obtained by the use of radioactively-tagged red cells injected intravenously combined with tissue analyses for hemoglobin and tagged red

cell content indicate that about one-fifth of the capillary blood becomes stagnant or trapped out of active circulation as the shock phase deepens.

4. The progressive decline in shock is not due to a progressive fall in plasma volume but to a progressive fall in the volume of actively circulating plasma.

5. The blood content in cubic centimeters per gram of tissue is not more and is generally the same, or less, in shock than it is in normal dogs.

6. The therapeutic problem in shock after adequate replacement of lost blood or plasma has failed is one of restoring volume and velocity flow through capillaries before the integrity of vital tissue processes is inevitably lost.

Acknowledgment is made to Miss Martha Goldberg for technical assistance.

Radioactive halogens were prepared by the Radiation Laboratories of the Massachusetts Institute of Technology and Harvard University.

BIBLIOGRAPHY

[1] Keeley, J. L., Gibson, J. G., and Pijoan, M.: The Effect of Thermal Trauma on Blood Volume, Serum Protein, and Certain Blood Electrolytes: An Experimental Study of the Effect of Burns. Surgery, **5**, 872–893, 1939.

[2] Seligman, A. M., and Fine, J.: Traumatic Shock I: The Production of Radioactive Plasma Proteins from Amino-Acids Containing Radioactive Sulfur. J. Clin. Invest., **22**, 265, 1943.

[3] Seligman, A. M., Rutenburg, A. M., and Banks, H.: Traumatic Shock II: The Preparation of Cystine, Methionine, and Homocystine Containing Radioactive Sulfur. J. Clin. Invest., **22**, 275, 1943.

[4] Seligman, A. M.: Traumatic Shock III: A Modified Electroscope Especially Suited for Measuring Substances with Low Engery Radiation. J. Clin. Invest., **22**, 281, 1943.

[5] Fine, J., and Seligman, A. M.: Traumatic Shock IV: A Study of the Problem of the "Lost Plasma" in Hemorrhagic Shock by the Use of Radioactive Plasma Protein. J. Clin. Invest., **22**, 285, 1943.

[6] Fine, J., and Seligman, A. M.: Traumatic Shock VIII: A Study of the Problem of the "Lost Plasma" in Hemorrhagic, Tourniquet, and Burn Shock by the Use of Radioactive Iodo-Plasma Protein. J. Clin. Invest. To be published.

[7] Gibson, J. G., Seligman, A. M., Evans, R. D., and Fine, J.: To be published.

[8] Swingle, W. W., Remington, I. W., Kleinberg, W., Drill, V. A., and Eversole, W. J.: An Experimental Study of the Tourniquet as a Method for Inducing Circulatory Failure in the Dog. Am. J. Physiol., **138**, 156, 1942.

[9] Fine, J., Fischmann, J., and Frank, H. A.: The Effect of Adrenal Cortical Hormones in Hemorrhage and Shock. Surgery, **12**, 1, 1942.

[10] Fine, J., Fischmann, J., and Frank, H. A.: Unpublished data.
Gregerson, M. I.: Personal communication.
Price, P. B., Hanlon, C. R., Longmire, W. P., and Metcalf, W.: Experimental Shock I Effects of Acute Hemorrhage in Healthy Dogs. Bull. Johns Hopkins Hosp., **69**, 327, 1941.

[11] Chambers, R., Zweifach, B. W., and Loewenstein, B. E.: Capillary Studies of the Mesentery of the Rat in Tourniquet Shock. To be published.

[12] Frank, H. A., and Fine, J.: Traumatic Shock V: A Study of the Effect of Oxygen on Hemorrhagic Shock. J. Clin. Invest., **22**, 305, 1943.

[13] Hahn, P. F., Ross, J. F., Bale, W. F., Balfour, W. M., and Whipple, G. H.: Red Cell and Plasma Volumes (Circulating and Total) as Determined by Radioiron and Dye. J. Exp. Med., **75,** 221, 1942.

[14] Ebert, C. V., and Stead, E. A.: Circulatory Failure in Acute Infections. J. Clin. Invest., **20,** 671, 1941.

[15] Page, I. H., and Abell, R. G.: The State of Vessels of the Mesentery in Shock Produced by Constricting the Limbs and the Behavior of the Vessels Following Hemorrhage. J. Exp. Med., **77,** 215–233, 1943.

[16] Long, C. H. N., and Engels, F. L.: Personal communication.

[17] Alexander, B., and Frank, H. A.: Personal communication.

[18] Lamson, P. D., Govier, W. M., and Greig, M. E.: Personal communication.

[19] Frank, H. A., Altschule, M. D., and Zamchek, N.: Traumatic Shock VII: The Effect of Paredrine on Dogs in Hemorrhagic Shock. J. Clin. Invest. In Press.

RÔLE OF THE NERVOUS SYSTEM IN SHOCK*

DALLAS B. PHEMISTER, M.D.
CHICAGO, ILL.

FROM THE DEPARTMENT OF SURGERY, UNIVERSITY OF CHICAGO, CHICAGO, ILL.

IT HAS BEEN GRADUALLY ESTABLISHED in comparatively recent years that the outstanding cause of surgical shock is the local loss of blood and/or plasma. The accompanying improvements in hemostasis and in the use of blood and plasma transfusions for the prevention and treatment of shock have resulted in marked improvement in surgical results, and in great extension of the field of operative surgery. Operations of great magnitude are now being successfully performed that were impossible before and cases of severe injuries and burns are being saved that previously were invariably fatal. These advances warrant further investigation of other causes of shock in the endeavor to obtain additional improvements in its prevention and treatment.

One of the oldest and most widely entertained theories is that shock may somehow be brought about by an insult to the nervous system. The influence of the nervous system on vasomotor tone may be briefly summarized as follows: Control is exercised through the vasomotor center in the medulla. Efferent impulses pass out from the vasomotor center by way of the spinal cord and sympathetic nerves to the blood vessels. They are both vasoconstrictor and vasodilator, but predominantly the former. Afferent impulses come to the vasomotor center over pathways from the somatic and the modulator or depressor nerves supplying the aortic arch and carotid sinuses and from the cerebral cortex. Both pressor and depressor impulses come from the somatic nerves and were shown, by Ranson and Billingsley,[1] to have separate pathways in the spinal cord. Both vasopressor and vasodepressor centers have been demonstrated in the cerebral cortex of monkeys and cats by Hoff and Green.[2] Impulses coming over the cardio-aortic or aortic depressor and carotid sinus modulator nerves are entirely vasodepressor.

The most popular conception of neurogenic shock is that it results from marked and prolonged lowering of blood pressure by afferent vasodepressor impulses coming to the medulla either from the injured field over somatic nerves or from the cerebral cortex, where they are set up as in syncope by adverse special sense or pain sense impulses or purely by mental action. Lowering of blood pressure is accomplished by inhibition of vasoconstrictor impulses and possibly, to some extent, by acceleration of vasodilator impulses. Cardiac inhibition is also a causative factor in syncope.

The great objection to this neurogenic theory of shock is the lack of evidence based on carefully controlled clinical studies and on concert experimental methods of production in which other factors, as local loss of circulating fluid, and anesthesia are excluded. It is well known, from animal

* Read before The American Surgical Association, May 13–14, 1943, Cincinnati, Ohio. The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Chicago.

experimentation,[3, 4, 5] that simple exposure and stimulation of somatic nerves of the limbs, as the sciatic and saphenous, by pinching, crushing, cutting or the application of an electric current of different strengths and frequencies, cause a variety of minor reactions but most frequently an initial reflex fall of blood pressure lasting for one to three minutes, after which the pressure may rise above or return to the previous level. The same has been found true for man, as in case of repeated crushing and pinching of the sciatic nerve during thigh amputation. Following alternating arrest and stimulation with a tetanizing current for one or two hours, the pressure may fall to some extent, but nothing like a state of shock is produced. The same fibers, large and small, are stimulated in the nerve trunks by these experiments as are stimulated in wounds of the extremities, and often much more forcefully. Seven rabbits have been tested during this study, and it was impossible to produce shock by these procedures. Upper abdominal operations[6] in man occasionally cause rapidly developing bradycardia and a fall of blood pressure to 80, 60 or 50 mm. Hg., but the patient remains in good condition, the pressure rises as the intra-abdominal manipulations diminish and the circulation returns to normal unless it has become embarrassed by other factors. The reaction has been explained by the assumption of vasodepressor fibers in the abdominal trunks of the vagi which are stimulated. Further study is indicated in order to determine more accurately the method of production. The marked lowering of blood pressure in fainting[6, 7] produced by the action of afferent impulses from the brain on heart and vasomotor center is also short-lived as loss of consciousness interrupts the adverse psychic impulses and produced recumbency with brain and heart coming to approximately the same level. Improvements of cerebral blood supply and elevation of blood pressure ensue and consciousness is regained within a relatively short time without harmful after-effects.

O'Shaughnessy and Slome,[8] and Kabat, Lorber and Welte,[9] have reported an increased tendency to shock production in case of limb trauma of dogs in which the limb was severed from the body except for the nerves and femur, and the circulation maintained either by perfusion with blood rendered noncoagulable or by crossed-circulation from another animal. However, Blalock and Cressman[10] did not confirm these results except to report that spinal anesthesia reduced the tendency to shock when general anesthesia was then induced by nembutal in cats and chloralose in dogs.

The cardio-aortic or aortic depressor nerves and the carotid sinus nerves are afferent nerves supplying the walls of blood vessels, stimulation of the endings of which by increase of the intravascular pressure causes a reflex fall in blood pressure, chiefly by inhibition of vasoconstrictor impulses from the vasomotor center in the medulla. In this way they serve to modulate blood pressure when it is by any mechanism elevated. Animal experiments have been carried out in which these nerves were stimulated in an effort to determine the effects of a purely neurogenic lowering of blood pressure except as modified by the anesthesia, blood loss from clot washings and

samples for analyses, and by the relatively slight trauma incident to the experiments. The results should be an index of vasodepressor action regardless of the source of the impulses.

Schachter, and the author,[11] have reported the results of stimulation of the carotid sinus nerves. In a minority of the experiments, the blood pressure could be maintained in the vicinity of or moderately below 70 mm. Hg. for hours, by continuous electrical stimulation using a bipolar cannula electrode inserted in the carotid sinus. Initial low shock levels were not obtained. Release of the stimulus at any time up to four or five hours was followed by a prompt rise of pressure to previous levels, but beyond that time both the response to release and the pressure during stimulation usually declined gradually, and death occurred in seven and one-half to nine hours with the animal in a state of shock. When blood pressure fell on stimulation but was maintained above 75 or 80 mm. Hg., there was remarkably little impairment of circulation, and the animals lived an average of ten hours longer than those with pressures maintained at 70 mm. Hg., or below, and only about ten hours less time than the control experiments.

Cardio-aortic Nerve Stimulation.—The cardio-aortic or aortic depressor nerves supplying the arch of the aorta and first portions of its large branches and some fibers to the heart, are more powerful depressor nerves than the carotid sinus nerves and offered a more favorable method of experimental neurogenic lowering of blood pressure. They are fused with the vagi in all animals except rabbits and a certain percentage of cats, for which reason rabbits were chosen for the experiments. Urethane 0.5 Gm. per Kg. body weight, was given intraperitoneally, which maintained light anesthesia. The femoral arteries were cannulated, one for kymographic recordings of blood pressure, and the other for drawing blood samples and for injections. The mandible was tied to the bit of the head piece of a dog-board on which the rabbit was fastened, the cardio-aortic nerves were isolated alongside the vagi in the neck and a shield electrode attached to a Harvard inductorium receiving six volts from a transformer was applied to each nerve. Blood pressure ranged from 90 to 120 with an average of 105 mm. Hg. Control animals with only the stimulus deleted lived 14 to 18.5 hours.

In favorable cases stimulation of both nerves, with the secondary coil at nine or ten centimeters from the primary, usually caused a sharp drop in blood pressure to a range of 25 to 60 mm. in two or three minutes and slowing of the pulse during the same period from an average rate of over 200 to a range of 60 to 100 per minute. A somewhat stronger stimulus was required to produce a similar effect if one nerve only was stimulated. With continued stimulation, the course of the blood pressure varied greatly according to the individual experiment. In some cases the pressure remained low for hours while in others it rose either rapidly or slowly. In such cases, increase of the strength of the stimulus usually caused a further decline. However, when a very marked decline was obtained by a weak stimulus, as with the secondary coil at nine or ten centimeters, increasing the strength of the stimuli to the

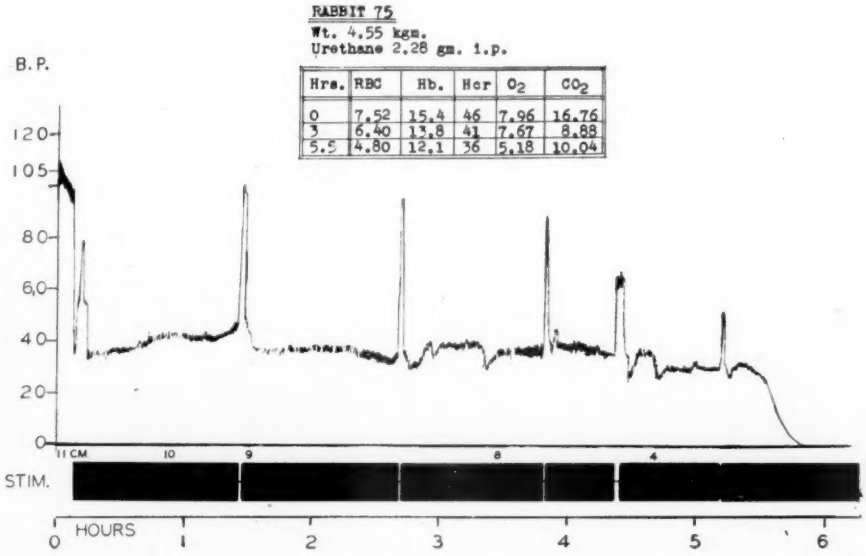


FIG. 1.—Death from low pressure after a 5.5-hour period of stimulation. Vasomotor center functioned well for four hours, and then gradually failed. Progressive hemodilution and reduction of arterial blood oxygen and carbon dioxide.

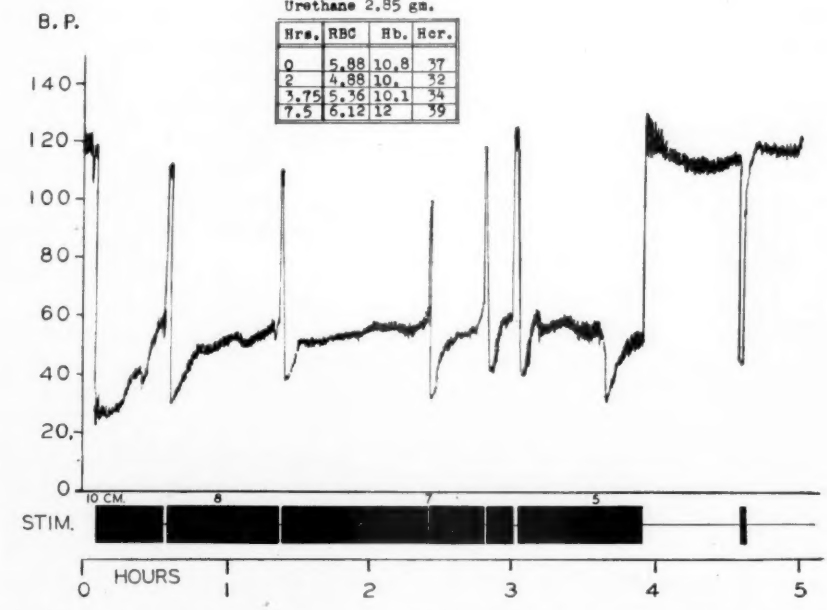


FIG. 2.—Under depressor nerve stimulation, blood pressure averaged 50 mm. Hg. for four hours. Vasomotor center never impaired and rapid recovery on stopping stimulus. Killed after 11 hours, with pressure at 90 mm. Hg.

maximum of the inductoriums failed to kill the animal, and might fail to cause further lowering of the pressure. The pulse always increased in rate after the initial few minutes, but usually continued somewhat reduced in rate as long as the blood pressure remained low from stimulation. Respirations were little influenced by the stimulus. Traumatism of the very small nerves during preparation, accumulation of blood in the wound and contact with tissues causing current leakage and drying of nerves, are variously responsible for the fluctuations in response.

Extensive experiments have been performed in which blood studies have been correlated with pressure studies and necropsy findings. They are being reported in detail by Laestar, Schafer, Eichelberger, Schachter, and the author, and only an abbreviated account is included here.

When the blood pressure was maintained at low levels by continuous cardio-aortic nerve stimulation, death took place in from 2.5 to eight hours and, in general, the lower the pressure the shorter the period of survival. In the majority of experiments, the pressure ranged between 35 and 55 mm. Hg., and the animals usually lived five to eight hours. Temporary release of the stimulus at intervals during the early and middle portions of the experiment usually resulted in a rapid rise of pressure to the vicinity of the previous level indicating a good state of vasomotor tone. But during the terminal portion (0.5 to 1.5 hours) of the period of survival, the response on release markedly weakened, indicating failure of the vasomotor tone and the blood pressure under stimulation usually declined slightly before death. Blood examination showed hemodilution and reduction of arterial blood oxygen and carbon dioxide. In some cases there was a tendency toward hemoconcentration toward the end. Figure 1 shows an experiment in which, for the first four hours, the blood pressure remained in the vicinity of 40 mm. Hg. during stimulation and rose to near the original level during the three short intervals when the stimulus was released. From then on, the pressure declined slightly during stimulation and the responses during the two releases had weakened rapidly before death at 5.5 hours. That is, the vasomotor tone was remarkably well preserved for four hours after which it gradually failed. Hemodilution progressed gradually throughout the experiment, except at times in the terminal stages.

When the vasomotor tone was well preserved, permanent release of the stimulus after such periods of depression lasting sometimes for four to seven hours would be followed by rapid restoration of blood pressure to the vicinity of the prestimulation level, and the animals lived on, similar to controls. The blood, which usually diluted during the period of low blood pressure, would show a tendency to concentrate after the pressure was again elevated. These findings are illustrated by Figure 2, in which experiment the blood pressure was maintained at a fluctuating level, averaging about 50 mm. Hg. for four hours, during which time there was marked elevation with each release. After dicontinuation of the stimulation, the blood pressure rose to the previous level, and seven hours later, when the animal was killed, it still registered

90 mm. Hg. The blood which had slightly diluted during the stimulation showed concentration at 7.5 hours, or 3.5 hours after restoration of the pressure following removal of the stimulus. This is evidence that the blood pressure may be maintained at shock levels for long periods by a purely nervous reflex vasodepressor mechanism, without serious impairment of either the vasomotor center in the medulla or the peripheral circulation and that the circulation may rapidly return to normal after stopping the stimulation. It is additional support of the finding of Roome, Keith and Phemister that a sudden low blood pressure produced without local loss of circulating fluid impairs the circulation less and is better tolerated than an equally low blood pressure produced by such loss.

In one animal the blood pressure starting at 106 mm. Hg. ranged between 55 and 80 mm. Hg. throughout the period of stimulation, and death did not occur until 13 hours had elapsed.

In a small percentage of experiments the blood pressure was reduced to levels of 30 to 40 mm. from the beginning, and there was usually a further gradual decline of pressure and a more rapid onset of failure of vasomotor tone, as indicated by poor recovery of blood pressure during temporary release of the stimulus. Continued stimulation would result in a serious condition of the animal or in death in less time than in the preceding group. Figure 3 shows an experiment in which the blood pressure fluctuated between 40 and 30 mm. Hg. during the first hour, and between 28 and 24 mm. during the following one and one-half hours, when death occurred. Vasomotor tone was greatly reduced after the first hour, as shown by brief releases of the stimulus then, and at the end of the second hour. There was progressive hemodilution, as shown by the reductions in red count, hemoglobin, hematocrit and plasma proteins. Arterial blood oxygen was considerably reduced and carbon dioxide strikingly so. This was one of the most rapid deaths that was produced by very low blood pressure from cardio-aortic depressor nerve stimulation, and both the failing vasomotor tone and the progressive hemodilution with reduction of blood oxygen and carbon dioxide were responsible for it. The cause of death in the animals dying with prolonged lowering of blood pressure to shock levels from nerve stimulation may well be designated as neurogenic shock. Slight degenerative changes have been found in the parenchymatous organs of some of the animals.

When the blood became considerably diluted and vasomotor tone showed signs of failure as a result of a long period of low blood pressure, produced by cardio-aortic nerve stimulation, the transfusion of either whole blood or plasma brought about a period of definite improvement of circulation. The level of blood pressure during stimulation was elevated little, or none, but the period of survival was prolonged, the response on release of the stimulus was improved, and the bleeding volume of the animal was approximately as great as that of controls. Thus, in one experiment the course was similar to that shown in Figure 3, and at the end of three hours the animal was almost moribund, with a blood pressure of 24 mm. Hg., which rose to only 38 mm.

on release of the stimulus. A blood transfusion of 20 per cent of the calculated blood volume, and 30-minute rest from stimulation, led to an elevation of blood pressure to 70 mm. Hg., and the rabbit then lived for seven hours, despite three one-hour periods of stimulation and lowering of blood pressure in the meantime.

Figure 4 records an experiment in which an extremely low blood pressure in the vicinity of 30 mm. Hg. was maintained for four hours, with progres-

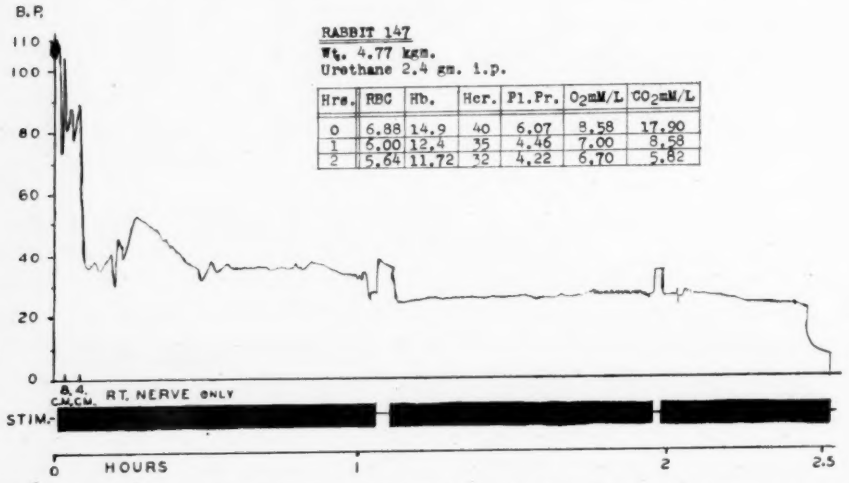


FIG. 3.—Marked and progressive vasodepression and early damage of vasomotor center, with death in 2.5 hours. Progressive hemodilution and reduction of blood, oxygen and carbon dioxide.

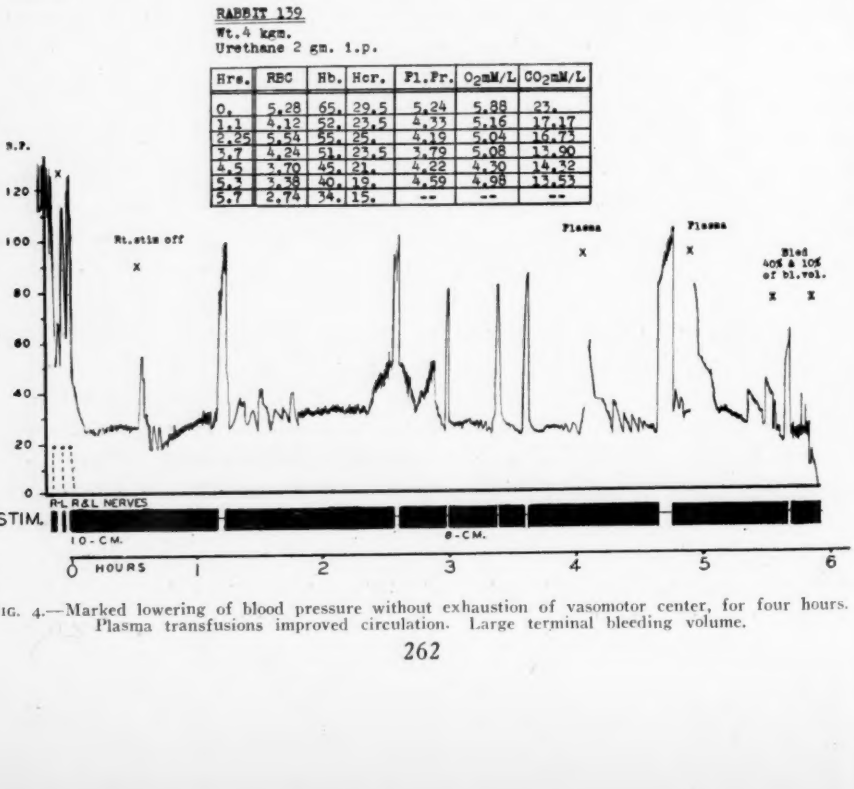


FIG. 4.—Marked lowering of blood pressure without exhaustion of vasomotor center, for four hours. Plasma transfusions improved circulation. Large terminal bleeding volume.

sive hemodilution and blood oxygen and carbon dioxide reduction, but with only moderate decline of vasopressor response on release of the stimulus. A 27-cc. plasma transfusion then raised the pressure only briefly, but release of the stimulus at 4.66 hours resulted in an increase in the level of elevation of blood pressure. A second 27-cc. transfusion at five hours further improved the circulation, and at 5.66 hours the animal was bled 40 per cent of the calculated blood volume during stimulation. The pressure was only moderately reduced by the bleeding and, on release of the stimulus shortly afterward, it rose to 60 mm. Hg., showing that the vasomotor center was still quite active. An additional ten per cent bleeding during stimulation was required to kill the animal. The plasma transfusions resulted in reductions in red counts and hemoglobin and hematocrit readings, but the increase in circulating volume and osmotic pressure prolonged life and improved the response of pressure on release of the vasodepressor stimulus.

Bleeding experiments were performed in order to test the effect of neurogenic lowering of blood pressure on animals that were already in a state of impending or actual shock as a result of hemorrhage. Clinically, severe hemorrhage followed by fainting, or by a fall of blood pressure from upper abdominal manipulation, might simulate the experiment. From 15 to 35 per cent of the calculated blood volume was withdrawn intermittently in a number of rabbits, reducing the blood pressure to 70 mm. Hg., or below. After the lapse of 15 to 40 minutes, the cardio-aortic nerves were stimulated and the blood pressure was, thereby, reduced to considerably lower shock levels. Usually, this resulted in some shortening of the survival period, as compared with controls, but the difference was not very great. Figure 5 is the record of an experiment in which, after testing the effects of cardio-aortic nerve stimulation, the animal was bled first ten per cent and then seven per cent of the calculated blood volume, which resulted in a blood pressure maintained at about 60 mm. Hg. 40 minutes later. Under stimulation, it was then maintained between 30 and 40 mm. Hg. for almost one hour before death occurred, with little pressor response on release of the stimulus shortly before. The blood which before showed slight dilution as a result of the hemorrhage, was concentrated near the end of the period of further depression under stimulation. It appears that the vasodepression from nerve stimulation shortened the survival time. However, in one case, when the blood loss was relatively small (15 per cent), the survival time, under further marked reduction of pressure by nerve stimulation, was remarkably long (seven hours).

In seven rabbits the effect on the circulation of lowering of blood pressure to levels averaging 40 to 50 mm. Hg. for periods of one to 4.33 hours by cardio-aortic nerve stimulation was tested by finding out how well bleeding was tolerated at the end of that time. It was found that the bleeding volume, which for seven controls averaged 42.5 per cent of the blood volume, estimated by the Evans blue dye method, varied from a moderate reduction to normal, the average being 39 per cent. This showed that although the

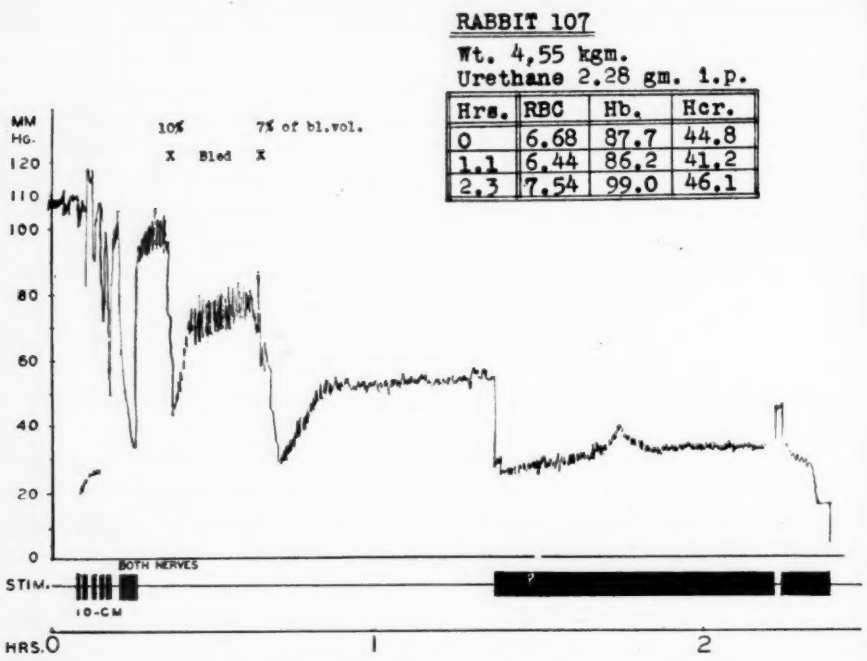


FIG. 5.—Shock produced by hemorrhage made worse by further lowering of blood pressure by aortic depressor nerve stimulation

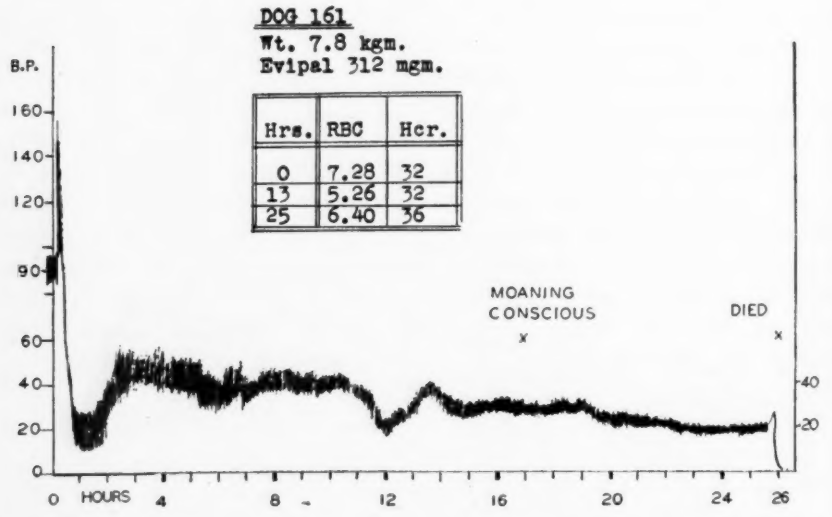


FIG. 6.—Section of spinal cord at C-7, with maintenance of circulation at remarkably low level for 26 hours before death

pressure was at shock levels, the circulation was, on the whole, remarkably well preserved.

The circulating blood volume during vasodepression was determined by Dr. Paul Schafer in five rabbits by the rather inaccurate Evans blue dye rapid method, drawing the five blood samples at ten minute intervals. The tests were made after two to three hours of stimulation and while the pressure was at shock levels. With the exception of the plasma protein in one experiment, a reduction in total volume, plasma volume and red cell mass was always obtained, the average being 17 per cent, 7 per cent and 34 per cent, respectively.

Further evidence that the blood pressure may be reduced to low shock levels for prolonged periods of time by a neurogenic mechanism before there is failure of the circulation has been obtained by the study of nine dogs with section of the lower cervical portion of the spinal cord. Under intravenous evipal anesthesia, 40 mg. per Kg. body weight, the femoral arteries were cannulated. One was used for drawing blood samples while the blood pressure was recorded continuously from the other. The spinal cord was then cut, aseptically, at the level of C-8 interrupting the sympathetic pathways from the vasomotor center in the medulla to the blood vessels and heart, and the animal followed until death. The stimulus of cutting the cord causes a brief rise in blood pressure and tachycardia which are followed by a sustained fall in blood pressure and bradycardia. Under the conditions of this experiment, the animals, with one exception, regained consciousness and remained in a quiet state of depression until coma supervened. The blood pressure varied with the experiment, but ranged between 70 and 20 mm. Hg., usually declining slowly until death took place in 25 to 33 hours. During the first 15 to 20 hours, the blood underwent dilution, after which it usually concentrated. Hemorrhage into the small intestine was usually found at autopsy, similar to that observed by Blalock[13] in dogs dying of shock produced by slow hemorrhage. Figure 6 records the findings in an animal in which the blood pressure dropped to the unusually low level of 20 mm. Hg. during the second hour, to recover to 50 mm. Hg. by the third hour, and then slowly declined to 20 mm. again, with death in 26 hours. The pulse rate varied between 90 and 60 per minute. Despite the low blood pressure, the animal remained partly conscious and occasionally moaned for 16 hours. The red cell counts showed a hemodilution during the first half of the experiment followed by hemoconcentration. The discrepancy in hematocrit readings is unexplained but may have been due to swelling of the red cells.

SUMMARY AND CONCLUSIONS

Neurogenic shock was produced by prolonged electrical stimulation of the cardio-aortic (aortic depressor) nerves of the rabbit resulting in marked and prolonged lowering of blood pressure, hemodilution anoxia and terminal exhaustion of the vasomotor center of the medulla. Usually there was a lapse of four to seven hours before serious impairment of the vasomotor

center and of five to eight hours before death. Removal of the stimulus before serious impairment of the center was followed by rapid recovery of the circulation. In exceptional experiments, the blood pressure was maintained at very low levels and the course was more rapid. The results serve as an index of the effect of hyperactivity of afferent vaso depressor impulses which would be the same regardless of the pathways over which they came to the medulla. The possibility that shock is ever produced by accidental injury of the cardio aortic nerves is so small that it scarcely merits consideration. Blood and plasma transfusions improved the condition of the shocked animals.

In dogs with section of the seventh cervical segment of the spinal cord, a remarkably severe and prolonged lowering of blood pressure resulted before there was failure of the circulation and death. These results demonstrate the marked capacity of the circulation to remain adequate when the blood pressure is lowered, principally by interference with vasoconstrictor nerve impulses to the blood vessels with relatively little associated blood loss.

Nothing remotely approaching this degree and duration of lowered blood pressure and failure of the circulation has been produced by direct stimulation of the somatic nerves. Consequently, it is highly improbable in accidental and operative wounds that shock ever results primarily, or even secondarily, from the action of afferent vasodepressor impulses passing over the somatic nerves that are injured in the field.

Vasomotor and cardiac afferent depressor impulses from the brain to the medullary center may lower blood pressure and produce syncopy but they act for too short a time to be the sole cause of shock in comparison with the long time required for its experimental production from an equally marked lowering of pressure by aortic depressor nerve stimulation. The same is true of the occasional reflex lowering of pressure in abdominal operations. However, when combined with hemorrhage, these may be contributing factors in shock production as were vasodepressor impulses from cardio-aortic nerve stimulation when preceded by hemorrhage to shock levels in these experiments.

A fuller realization on the part of the surgeon of the relatively small importance of hyperactivity of afferent depressor nerve impulses and of the relatively great importance of blood and plasma loss and toxicity of anesthetics in the causation of surgical shock, will lead to greater attention to the latter factors and to further improvement in surgical therapy. The primary cause of shock is probably never a purely reflex vasodepressor reaction.

REFERENCES

[1] Ransom, W. S., and Billingsley, P. R.: Afferent Spinal Path for Depressor Reflex: Studies in Vasomotor Reflex Arcs. V. Amer. Jour. of Phys., **42**, 0, 1916.

[2] Hoff, E. C., and Green, H. D.: Cardiovascular Reactions Induced by Electrical Stimulation of The Cerebral Cortex. Amer. Jour. of Phys., **117**, 411, 1936.

[3] Mann, F.: The Peripheral Origin of Surgical Shock. Johns Hopkins Hosp. Bull., **25**, 207, 1914.

[4] Ewing, E. M., and Janeway, H. H.: Annals of Surgery, **59**, 162, 1914.
[5] Porter, W. T.: Harvey Lecture: Vasomotor Relations. Boston M. and S. Jour., **158**, 73, 1908.
[6] Phemister, D. B., and Livingstone, H.: Primary Shock. Annals of Surgery, **100**, 714, 1934.
[7] Cotton, T. F., and Lewis, T.: Observations on Fainting Attacks Due to Inhibitory Cardiac Impulses. Heart, **7**, 23, 1918.
[8] O'Shaughnessy, L., and Slome, D.: Etiology of Traumatic Shock. British Jour. of Surg., **22**, 589, 1935.
[9] Lorber, V., Kabat, H., and Welte, E. J.: Nervous Factor in Traumatic Shock. Surg. Gyn. and Obst., **71**, 469, 1940.
[10] Blalock, A., and Cressman, R. D.: Experimental Traumatic Shock: Further Studies Particularly with Reference to the Role of Nervous System. Surg. Gyn. and Obst., **68**, 278, 1939.
[11] Phemister, D. B., and Schachter, R. J.: Neurogenic Shock. I. The Effects of Prolonged Lowering of Blood Pressure by Continuous Stimulation of the Carotid Sinus in Dogs. Annals of Surgery, **116**, 610, 1942.
[12] Roome, N., Keith, W., and Phemister, D. B.: Experimental Shock: The Effect of Bleeding After Reduction of the Blood Pressure by Various Methods. Surg. Gyn. and Obst., **56**, 161, 1933.
[13] Blalock, A.: Acute Circulatory Failure. Surg. Gyn. and Obst., **58**, 551, 1934.

Discussion.—Dr. Alfred Blalock (Baltimore): These are two excellent papers. Dr. Phemister and I, and others, have maintained for a good many years that the most important agency in the initiation of traumatic shock is the regional loss of fluid from the blood stream. Most of the pathologists and the physiologists have maintained that there is a general increase in capillary permeability even in the early stages of shock.

Now Doctor Fine and his group, Gregersen and Root, at Columbia, Gibson and Aub, in Boston, Evans, of Richmond and others, have come to the conclusion that there is not a general increase in capillary permeability in traumatic shock even in the terminal stages. Even though I can find no flaw in their experiments, it is difficult for me to accept this whole-heartedly. It would appear that in the terminal stages there should be a general increase in capillary permeability, but, as I say, the evidence points in the other direction.

I hope that Doctor Fine, and others, are correct in their findings, because it makes for a more hopeful outlook in therapy. Certainly, the inability to establish any definite beneficial effect from the use of adrenal cortical extract would indicate that they are correct.

Perhaps several remarks regarding the three prevailing theories on traumatic shock would not be out of order; namely, the regional fluid loss, the nervous influences, and the toxemia theory.

First, as regards the regional loss of fluid, I would agree with what Doctor Phemister said in his introduction. The importance of this in most cases of shock has been established and the beneficial effects of the use of blood and blood substitutes have been shown. It would appear that further study along this line should be in connection with the finding of other blood substitutes, such as perhaps Doctor Lockwood will talk about this morning.

Secondly, as regards the rôle of the nervous system in shock, this has been covered by Doctor Phemister. It would appear that studies along this line would not be extremely hopeful as making for better therapy. At least it seems that attempts to block nerves have not resulted in much benefit in the treatment of traumatic shock. Certainly, the use of spinal anesthesia is not advised in the treatment of traumatic shock due to injuries to the lower extremities so it would appear that further researches along this line would not be particularly hopeful. This is not saying that the nervous system has nothing to do with the genesis of traumatic shock.

Thirdly, as regards the so-called toxemia theory, or what perhaps today had

better be spoken of in terms of metabolic disturbance, perhaps the future outlook is somewhat better, for it does appear very likely that there are chemical hormonal disturbances that might be treated successfully.

The results of Doctor Fine in this connection are exceedingly interesting, as are those of C. N. H. Long, of Prinzmetal, and of many other investigators.

In other words, as Doctor Phemister has said, it appears that the regional fluid loss factor is now fairly generally appreciated, and one can use blood and blood substitutes and other agencies, such as Doctor Elman spoke of yesterday, to correct this condition. At least from the experimental viewpoint it would appear to me that our energies should now be directed toward this third point, whether it be a toxemia or whether it be the chemical disturbances, and try to find an accessory means of improving our present knowledge on the treatment of this condition.

Again I want to say how much I enjoyed these two excellent papers, and they represent the work of two groups out of approximately forty-five different groups in this country who are studying shock.

DR. JACOB FINE (closing): It is difficult to find one's way in the literature on shock because of contradictory evidence from equally competent investigators. These contradictions are frequently due to differences in the experimental conditions, the significance of which often are not sufficiently evaluated. The literature on tourniquet shock, in particular, is a good example. Nearly all the recent studies on this type of shock indicate that recovery is seldom achieved even with large transfusions of plasma or other blood substitutes. Our own experience, however, is that recovery from tourniquet shock is the usual result from the transfusion of plasma or other blood substitutes. The reason for this difference in the result is that in our dogs no anesthesia, except morphine, was used, while barbiturate anesthesia, which is known to be capable of aggravating the state of shock, has been uniformly used by other investigators. Thus, Mylon and Winternitz (Am. Jour. Phys., June, 1943), using nembutalized dogs, found that tourniquet shock (tourniquets to both hind limbs for five hours) if untreated, is uniformly fatal. When we produced this type of tourniquet shock (*i.e.*, tourniquets for five hours to both hind limbs) using morphine alone, the dogs commonly failed to go into shock. When they treated such dogs with plasma albumin no beneficial effect was obtained, but cure was achieved with sodium succinate and saline solution. The cure achieved by sodium succinate and saline solution may well have been due to the neutralizing by succinate of the effect of nembutal on tissue respiration, thus permitting spontaneous recovery, as in our own unanesthetized dogs. The fact that their dogs, if untreated, uniformly died does not mean that tourniquet shock (for five hours to both hind limbs) is uniformly fatal. It does mean that this type of tourniquet shock *plus nembutal anesthesia* is uniformly fatal.

DR. DALLAS B. PHEMISTER (closing): I only want to say that one of the ideas that should be gotten out of the head of the average member of the medical profession is the traditional fixed one that shock may be produced by afferent vasodepressor nerve influences. I am not discussing other neurogenic theories.

SURGICAL GUT (CATGUT) TUBING FLUID AS A TISSUE IRRITANT*

CHARLES LITTLE DUNHAM, M.D., AND HILGER PERRY JENKINS, M.D.
CHICAGO, ILL.

FROM THE UNIVERSITY OF CHICAGO, SCHOOL OF MEDICINE, CHICAGO, ILL.

IN AN extensive study of the absorption of surgical gut (catgut), recently published by Jenkins, and coworkers,[1] a point of considerable interest was the noticeable variation in the magnitude of the tissue reaction which was observed in tissue implantation tests of surgical gut products from different commercial sources. Those products which had a tendency to produce the more conspicuous tissue reactions were usually observed to undergo a more rapid loss of tensile strength and frequently a more rapid rate of complete absorption than products which produced a less conspicuous tissue reaction. Relatively rapid absorption was generally found to be associated with a predominantly leukocytic reaction, to which the gut appeared to be especially vulnerable. Relatively slow absorption was associated with a predominantly macrophage response which appeared after an initial leukocytic invasion of varying magnitude which in some instances was relatively negligible. Although it was generally found that the surgical gut from certain sources tended to produce conspicuous reactions while minimal reactions were observed with products from other sources, there were many exceptions encountered.

On the basis of the observations made, there appeared to be some unexplained factor which contributed to the magnitude of the tissue reactions observed. This factor was not apparently an inherent property of the gut *per se* because it was not constant in all products. This prompted us to explore the possibilities of the presence of a tissue irritant in the tubing fluids commonly used for surgical gut, which, if carried into the tissues along with the gut, could explain many of the reactions observed. This study concerns itself with the two general classes of tubing fluids, namely, the anhydrous liquids used for boilable gut, and the alcoholic solutions used for the nonboilable surgical gut.

BOILABLE PRODUCTS

Many manufacturers have used xylene (xylol) as a tubing fluid for their boilable products because this is a completely anhydrous liquid and does not cause any damage to the gut when the tubes are subjected to boiling or autoclaving for surface sterilization of the glass before use in the operating room. Furthermore, the manufacturers can heat-sterilize the surgical gut after sealing

*Read by title before the American Surgical Association, May 13–14, 1943, Cincinnati, Ohio.

the tubes if they use an anhydrous liquid such as xylene. Some manufacturers have, at one time or another, used toluene (toluol) instead of xylene.

EXPERIMENTS

1. An intradermal injection of 0.025 cc. of xylene tubing fluid, obtained from a commonly used boilable product, was made in the skin of the forearm of one of us. Within six hours there was a red, tender welt, 0.5 cm. high and 4.0 cm. in diameter, at the site of the injection. The reaction was extremely painful and subsided over a period of one week. There was no superficial necrosis. The lesion resembled an acute cellulitis such as one sees produced by streptococcus infections.

FIG. 1.—Showing tissue necrosis 48 hours after intradermal injection of 0.05 cc. amounts of (*A*) xylene (A.C.S.), (*B*) Toluene (A.C.S.), (*C*) xylene tubing fluid, and (*D*) hi-flash solvent, into the back of a dog. Ulceration of the necrotic skin has occurred in all except the toluene injection.

2. Intradermal tests were carried out on a series of animals using 0.05 cc. of xylene (A.C.S.), toluene (A.C.S.), and xylene which had been used as a tubing fluid for surgical gut. In a few experiments white rats and rabbits were used, but it was found that the skin of the back of dogs, being less delicate, was more satisfactory for this work. The immediate reactions to the injections were relatively slight. By the end of an hour one could see only a pale, slightly elevated wheal 1 to 2 cm. in diameter, but by the end of 18 hours permanent tissue damage had occurred. The xylene (A.C.S.) regularly produced necrotic lesions 1 to 2 cm. in diameter surrounded by an edematous and reddened inflammatory margin several millimeters wide. Xylene tubing fluid appeared to produce somewhat more conspicuous lesions than standard laboratory xylene (A.C.S.). Sloughing of the necrotic areas followed in a few days. Toluene (A.C.S.) produced less severe reactions and in most instances these were ultimately not much greater in magnitude than those described below as characteristic of 95% ethyl alcohol (Fig. 1).

3. Intradermal tests were carried out in dogs using 0.05 cc. of varying concentrations of xylene and toluene (1, 5, 10, 15 and 50 per cent by volume) in 95% ethyl alcohol. Control injections using 95% ethyl alcohol produced an immediate coagulation of the tissues, surrounded by erythema. The lesions did not progress and the erythema tended to subside rapidly. These lesions rarely exceeded 1 cm. in diameter, and were usually 0.5 cm. or less, their size

being determined largely by variations in the technic of injection, especially the depth of penetration of the needle. The more superficial the injection the greater the tendency to spreading, with the result that the lesion produced would have a greater diameter. It should be mentioned here that the same amount of alcohol (0.05 cc.) injected into the human skin usually produced only relatively transient lesions which were negligible after a day or two. The mixtures of xylene and toluene in alcohol characteristically produced an immediate coagulation of the tissues at the site of injection, with the development progressively of erythema and appreciable necrosis for the higher concentrations of the solvents in alcohol. Injections of 50% xylene and 50% toluene in alcohol produced lesions which were of a greater magnitude than were observed with undiluted xylene or toluene, respectively. The mixtures with lower concentrations of xylene or toluene in alcohol produced lesions somewhat more striking than the alcohol controls, the magnitude varying in proportion to the concentration of xylene or toluene.

NONBOILABLE PRODUCTS

The tubing fluids used for nonboilable surgical gut have been alcoholic solutions, usually 95% or 96% ethyl alcohol plus a small amount of some germicidal agent. The compositions of the tubing fluids of the various manufacturers may vary to some extent from time to time. In recent years the following formulae have been used:

Ethyl alcohol 95%, with phenyl mercuric benzoate 0.02% or potassium mercuric iodide 0.3% or 0.1%.
Ethyl alcohol 96%, with phenyl mercuric benzoate 0.1% or potassium mercuric iodide 0.2%.
Ethyl alcohol 76% and isopropyl alcohol 20%, with potassium mercuric iodide 0.06%.
Alcohol, anhydrous and methanol 3% to 14% and in certain products 0.8% to 2.5% iodide.

The alcoholic solution which contains 4 to 5% of water renders the surgical gut pliable, so that it can be used for suturing as soon as the tube is opened without having to resort to the wetting procedures required for rendering boilable products pliable. In one product anhydrous alcohol was used with varying amounts of methanol. The presence of the latter apparently induces pliability in the absence of water. These alcoholic solutions seriously damage the gut if the tubes are heated and, therefore, it is necessary to surface sterilize the glass by chemical agents instead of by boiling or autoclaving. The sterility standard of the gut within the tubes is fundamentally the same for nonboilable products as for the boilable, because extensive heat sterilization has been carried out in an anhydrous liquid just as is done for boilable gut. The liquid used for heat sterilizing is then removed to a greater or less extent from the tubes, the alcoholic solution is added and the tubes sealed.

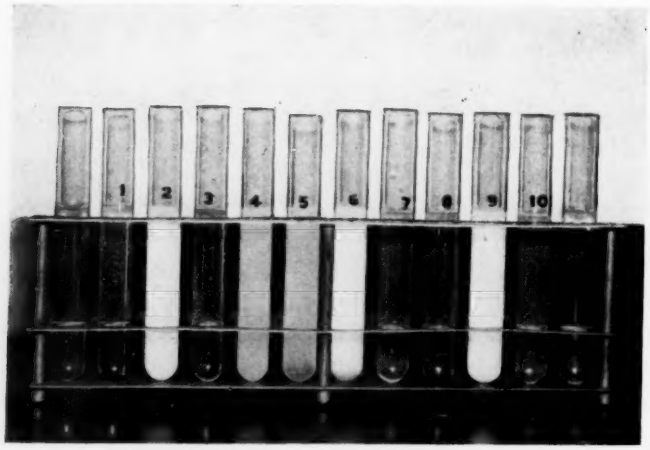


FIG. 2.—Showing the "emulsion test" on nonboilable surgical gut tubing fluid of ten different companies. To 0.5 cc. of alcoholic tubing fluid 5 cc. of water were added. Definite evidence of emulsion is shown for Companies II., IV., V., VI., and IX. A very slight clouding suggestive of a trace of water-insoluble component is shown for Companies I., VII., VIII., and X. The tube for Company III. is practically as clear as the alcohol-water controls at each end of the rack (tubes without number)

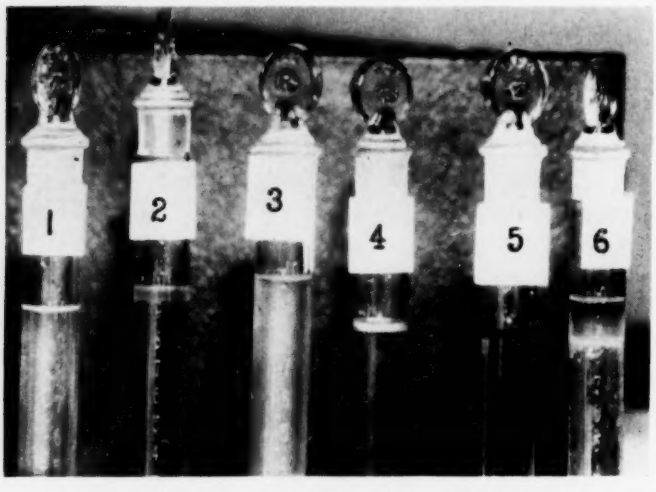


FIG. 3.—Showing supernatant water-insoluble liquid obtained from the alcoholic tubing fluid of the nonboilable surgical gut of six different companies. To 10 cc. of tubing fluid in 100 cc. cassia flasks (lower bulbous portion of flask not shown) water was added to produce emulsion and this was acidified with concentrated H_2SO_4 to expedite separation of water-insoluble component, the amount of which could then be read off as tenths of a cubic centimeter in the graduated neck of the flask, each tenth of a cubic centimeter representing 1%. In this test there was 4 to 15% of water-insoluble liquid recovered from four of the products, while in two products none was obtained

EXPERIMENTS

4. During the course of the previously mentioned study of the absorption of surgical gut[1] it was noticed that certain of the alcoholic tubing fluids became white upon the addition of water. The full significance of this observation was not appreciated at the time. Subsequent examination under the microscope of the white fluid produced by the addition of water to the alcoholic tubing fluid revealed minute globules of varying size which exhibited characteristic brownian movement. It was obvious, therefore, that we were dealing with an emulsion produced when the alcoholic solution was diluted with water, thus revealing the presence in the alcoholic solution of a water-insoluble liquid component. The presence of such a component has not been mentioned by the manufacturers on the package labels.

A simple test was devised for determining whether appreciable quantities of this water-insoluble component were present in the alcoholic tubing fluid. The addition of 5 cc. of distilled water to 0.5 cc. of tubing fluid produced a creamy emulsion when there was much of this material present. This was considered a positive test. If the solution remained clear it was considered negative. If a slight turbidity appeared it was considered as indicating a trace of water-insoluble liquid. A number of tests were run on samples of tubing fluids from the products of ten different manufacturers. The tubing fluids of five of these companies gave strongly positive reactions to this test (Fig. 2).

5. We next attempted to separate the water-insoluble component from the rest of the tubing fluid in order to get a rough idea of how much of it was present. We were able to do this by acidification. Ten cubic centimeters of tubing fluid from each of six different companies was placed in separate cassia flasks and diluted with 85 cc. of distilled water. Five cubic centimeters of concentrated sulphuric acid was then added, and the flasks securely stoppered and shaken. A conspicuous emulsion appeared in four of the six flasks, while the fluid in the other two remained only slightly turbid. At the end of a few days the water-insoluble material had collected as a supernatant layer in the graduated necks of the four flasks which had contained the heavy emulsion. The amount of supernatant liquid varied from 0.4 cc. to 1.5 cc. This would indicate concentrations of water-insoluble material in the alcoholic tubing fluids of from 4.0 to 15.0 per cent in these four products (Fig. 3).

6. The cooperation of an independent chemical laboratory was obtained in an endeavor to get more exact information about the nature and amount of this water-insoluble component which we had found in certain of the alcoholic tubing fluids. The report of this phase of the work will be made independently by Albert E. Sidwell, Jr. (ANNALS OF SURGERY, **118**, 285, August, 1943).

We obtained from this source specimens of the water-insoluble components which had been recovered by fractional distillation. The relatively high boiling range of these materials (140° to 190° C.) was of particular interest. This material was used by us in subsequent experiments for titration and intradermal tests.

7. The "emulsion titration test" was devised to obtain some quantitative data on the water-insoluble component in the alcoholic tubing fluid of individual tubes of nonboilable surgical gut. This is based upon the saturation point of water-alcohol mixtures for water-insoluble liquids which are soluble in alcohol. This consists of titrating two cubic centimeters of alcoholic tubing fluid with distilled water. The end-point is considered to have been reached when a persistent cloudiness from the emulsion occurs. The amount of

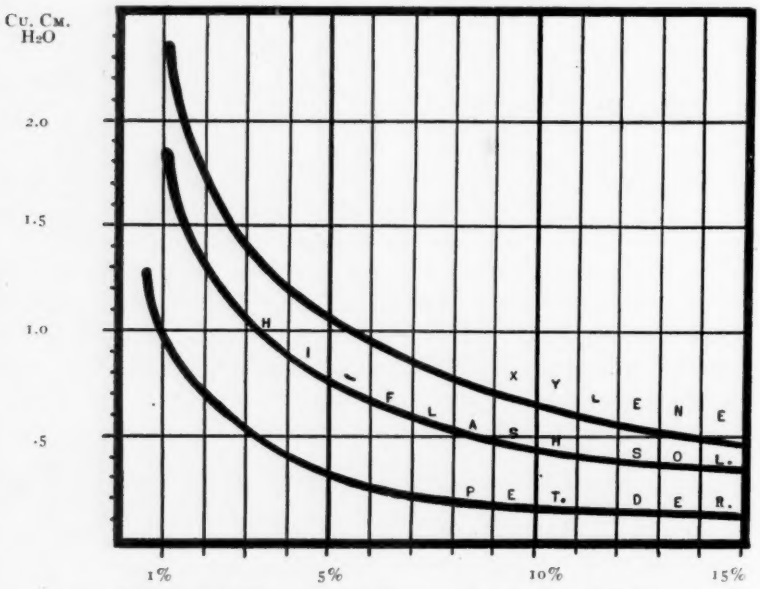


FIG. 4.—Showing solubility of xylene, hi-flash solvent, and a petroleum derivative in varying water—alcohol mixtures. The curves were derived from saturation points of different concentrations of these solvents in various water—alcohol mixtures expressed in terms of the number of cubic centimeters of distilled water which must be added to the various concentrations of these solvents in 95% alcohol to produce emulsion. The curve for hi-flash solvent is practically superimposable on that for the high boiling point distillate recovered from alcoholic tubing fluid (Table I).

water required to produce the emulsion must then be interpreted from a graph prepared by titrating known concentrations of the water insoluble liquid in alcohol such as is demonstrated in Figure 4. The interpretation of the amount of water-insoluble component present depends, therefore, on the nature of the water-insoluble liquid (Table I). The curve for hi-flash solvent* obtained by titrating known amounts in alcohol was found to be practically superimposable on that for the high boiling range fraction which was isolated by Sidwell from pooled alcoholic tubing fluid of recent manufacture. Therefore, the results of the titrations in terms of distilled water may then be interpolated into per cent of hi-flash solvent in the fluid. (Table II). These results cannot be construed as representing quantitative analyses, but rather an approximation of the water-insoluble component be-

* Hi-flash solvent, boiling range 163° C. to 180° C., an anhydrous hydrocarbon coal tar derivative supplied to manufacturers for the purpose of heat sterilization of catgut.

lieved to be present. These results, however, have been comparable to the emulsion separation tests as well as to the results described by Sidwell. Over 175 tubes of nonboilable catgut were subjected to this "emulsion titration test."

TABLE I

Cc. H_2O Required for Titration to Produce Emulsion

% Solvent in Alcohol	Toluene	Xylene	T. F. Dist.	Hi-flash	Pet. Der.
1	*	2.35	1.92	1.66	0.93
2.5	2.4	1.5	1.12	1.13	0.51
5	1.6	1.05	0.68	0.76	0.30
10	1.0	0.65	0.45	0.42	0.15
15	0.65	0.45	0.35	0.31	....

Emulsion Titration Test: Titrations with distilled water of 2 cc. aliquots of various concentrations in 95% ethyl alcohol C.P. of toluene, xylene, pooled tubing fluid distillate, hi-flash solvent and the petroleum derivative.

TABLE II

AMOUNT OF WATER REQUIRED TO PRODUCE EMULSION IN 2 CC. OF ALCOHOLIC TUBING FLUID, AND THE INTERPRETATION OF THESE RESULTS IN TERMS OF PERCENTAGE OF WATER-INSOLUBLE COMPONENT (W.I.C.)

(*Maximum-Minimum Range*)

	Series 1941-42		Series 1939-40		Series 1938	
Company	H_2O	W.I.C.	H_2O	W.I.C.	H_2O	W.I.C.
I.....	1.32 cc.	2.0%	1.5 cc.	1.5%	2*	Trace
	2*	Trace	2*	Trace	2*	Trace
II.....	.62 cc.	6.5%	.45 cc.	10%	.44 cc.	10%
	.91 cc.	4.0%	2* cc.	Trace	2* cc.	Trace
III.....	1.1 cc.	3%	.63 cc.	6.5%	.82 cc.	4.5%
	2* cc.	Trace	2* cc.	Trace	2. * cc.	Trace
IV.....	.91 cc.	4%	.21 cc.	7.0%	.23 cc.	6.5%
	1.42 cc.	1.5%	.64 cc.	2.25%	.87 cc.	1.2%
V.....	.47 cc.	9.5%	.52 cc.	8%	.64 cc.	6%
	2. * cc.	Trace	2* cc.	Trace	2. * cc.	Trace
VI.....	.35 cc.	14%	.24 cc.	?	.2 cc.	?
	.71 cc.	6%	.50 cc.	?	.47 cc.	?

*2 means 2 cc. or more of water.

The W.I.C. was interpreted from the graph in Fig. 4 using the curve which was characteristic of hi-flash solvent because the solubility curve of the water insoluble component recovered from most products closely resembled that of hi-flash solvent.

In one product the results of the titration test were interpreted in terms of petroleum derivative, which was believed to be the water-insoluble liquid during certain years.

In another product the titration tests were not evaluated for past years because data on the nature of the water-insoluble component was not available.

The "Emulsion Titration Tests" showed that over a considerable period of time there has been an appreciable amount of water-insoluble liquid present in alcoholic tubing fluid of most nonboilable surgical gut products. This has ranged from a trace to up as high as 10% in some products, while in one product it ranged from 6 to 14%. In some instances it ranged from a trace to 6%, or a trace up to 2%. There was considerable variation in tests made on the same product, as well as on different tubes in the same package lot. It was of interest to find that in one series of tests on one product, all tests showed not more than a trace, while in a subsequent series on this product, 12 out of 15 tests showed only a trace.

8. Injection experiments were devised to ascertain whether the water-insoluble liquid found in the alcoholic tubing fluids of nonboilable products

was irritating to the tissues. Intradermal injections of 0.05 cc. of the alcoholic tubing fluids of six different manufacturers were made in the backs of three human subjects. Control injections were made with 95% ethyl alcohol. The alcohol injections produced an immediate whitening of the tissues at the site of injection. This was from 3 to 5 mm. in diameter. About it there developed, in a matter of minutes, a wheal 1.0 to 1.5 cm. in diameter surrounded, in turn, by an erythematous flare approximately 2 cm. across. This reaction reached

FIG. 5.—Showing irritant action of alcoholic tubing fluids of six different nonboilable products as compared with 95% ethyl alcohol, by intradermal tests (0.05 cc.) in Subject J. after 24 hours. Maximum reaction was observed for Companies II, V, and VI. Moderate reaction was seen for Company IV, and slight reactions for Companies I and III. The least reactions were obtained with 95% ethyl alcohol controls. Compare the magnitude of the tissue reaction here with the amount of water-insoluble component demonstrated in Figures 2 and 3, for the several products tested.

its maximum in one-half hour and then gradually subsided over a period of several hours. In many of the tests there was only slight evidence of reaction after 24 hours, although in one test there was produced a small area of necrosis, 2-3 mm. across, which subsequently ulcerated. In contrast to the action of pure alcohol, the alcoholic tubing fluids produced immediate reactions similar in character to the above but of a greater magnitude, and at the end of 24 hours they had all produced lesions in which the central white area persisted and, regularly, lead to actual necrosis and subsequent ulceration. Furthermore, the surrounding tissues for a matter of several millimeters to more than a centimeter were red and inflamed (Figs. 5 and 6). A comparison of Figure 6 with Figure 2 and Table II brings out rather strikingly the tendency for those tubing fluids which contained an abundance of water-insoluble component to produce the largest skin reactions. In some instances the lesions after undergoing ulceration required more than a month to heal over.

9. The pooled high boiling point distillate referred to above (Exper. 7) was also used for intradermal injections. Five-hundredths of one cubic centimeter of this material in concentrations of 1, 5, 10 and 15 per cent in 95% ethyl alcohol was injected into the skin of the back of a human subject.

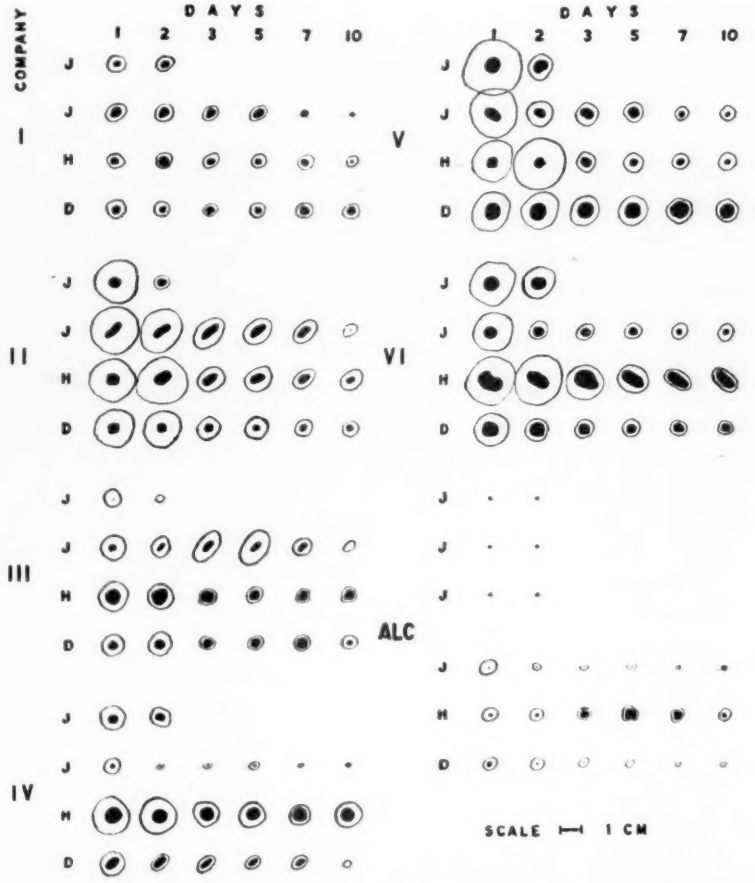


FIG. 6.—Scale drawing showing the variation in the tissue reaction obtained by intradermal injection (0.05 cc.) of various alcoholic tubing fluids and pure 95% alcohol from one to ten days after injection. The skin of the back of three human subjects was used. The alcoholic tubing fluids were obtained from the nonboilable surgical gut of six different manufacturers, indicated as Companies I, II, etc. The area within the circle represents erythema, the solid black center represents necrosis. The alcoholic tubing fluids of Companies II, V, and VI, appeared to be the most irritating while those of Companies IV, III, and I, were less irritating. All of these alcoholic tubing fluids were more irritating than pure 95% alcohol. The magnitude of the tissue reaction appears to correlate with the amount of water-insoluble component present in these products as demonstrated in Figures 2 and 3.

The magnitude of central necrosis and peripheral inflammatory reaction varied in proportion to the amount of distillate present. The alcohol produced a minimal lesion which had almost subsided on the day after injection. The higher concentrations produced lesions which required several weeks to heal. Concentrations as low as one per cent of this high boiling range fraction of alcoholic tubing fluids are definitely necrosing in alcoholic solution. The

lesions produced were similar in all respects to those produced by the alcoholic tubing fluids themselves (Fig. 7).

10. Similar intradermal tests were performed upon dogs, using small amounts (0.025 to 0.05 cc.) of undiluted high boiling range distillates recov-

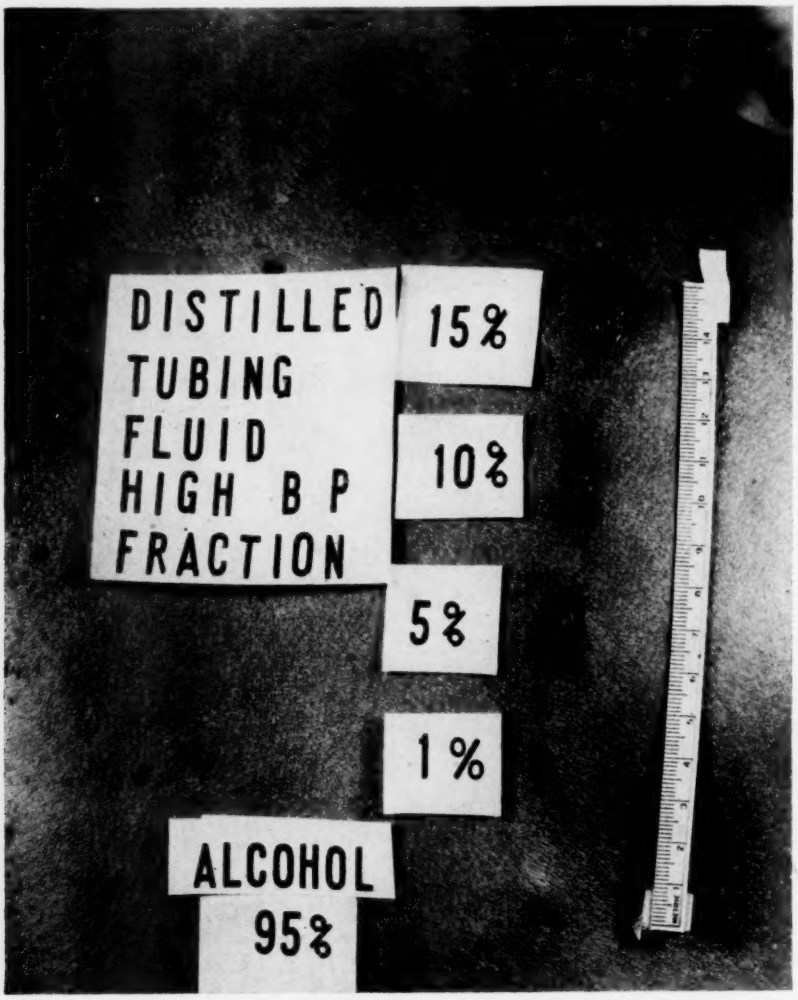


FIG. 7.—Showing intradermal tests (0.05 cc.) on Subject J, at 24 hours, using known concentrations in 95 per cent ethyl alcohol of a mixture of high boiling range (140°-150°C.) water-insoluble material obtained by distillation of nonboilable alcoholic tubing fluids. In concentrations as low as one per cent, this water-insoluble liquid produces irritation of a greater magnitude (erythema and necrosis) than the 95 per cent ethyl alcohol control (erythema which has almost subsided). The lesions produced by the 5, 10, and 15 per cent concentrations compare with those in Figure 5.

ered separately from five products. All five distillates produced necrotic lesions, approximately 2 cm. in diameter, which subsequently sloughed and ulcerated. The immediate reactions resembled those characteristic of xylene, and it was not until the following day that the potent necrosing action of the

materials was apparent. There was no appreciable difference in the magnitude of the reaction produced by the distillates from the five different products. They all appeared to be somewhat more potent irritants and necrosing agents than xylene.

11. Intradermal tests were performed upon dogs with undiluted hi-flash solvent and with the material referred to in Experiment 7 as petroleum derivative, and which was believed to represent the water-insoluble component present in the tubing fluid during certain years of at least one brand of non-boilable gut. Hi-flash solvent behaved exactly like the undiluted distillates used in Experiment 10, producing on the second day large necrotic lesions which subsequently sloughed and ulcerated. The petroleum derivative produced the same end-result, the only difference noted being a hemorrhagic appearance of the necrotic area prior to its breakdown. Both of these solvents appeared to be more damaging to tissues than xylene tubing fluid.

Tests with various concentrations of these materials in 95% alcohol were also made on dogs. Hi-flash solvent was used in concentrations of 1, 5, 10, 15 and 50 per cent, while the petroleum derivative, which is not freely soluble up to 50 per cent in alcohol, was used in concentrations of 1, 5, 10, 15 and 25 per cent. Hi-flash solvent, 50% in alcohol, and petroleum derivative, 25% in alcohol, produced lesions of a definitely greater magnitude than when undiluted. In these experiments upon dogs' skin, which is much more susceptible to the action of 95% alcohol than is human skin (Exper. 3), it was sometimes difficult to distinguish the lesions produced by the 1 and 5% concentrations from those produced by the alcohol controls. The 10 and 15% concentrations, however, produced lesions obviously greater than those produced by 95% alcohol.

12. Intradermal injections were made in dogs using varying concentrations of the germicidal agents used by manufacturers for their alcoholic tubing fluids. The lesions produced were difficult to distinguish from pure 95% alcohol controls. Phenyl mercuric benzoate is quite insoluble in water and therefore, could not be tested in aqueous solution. Tests using potassium mercuric iodide, 0.3% in saline, produced a relatively small area of edema in the skin of rabbits but no evidence of necrosis was obtained. These tests do not exclude the germicidal agents as a source of some irritant action in the tissues. Such action, if any, however, is negligible in comparison with that of the potent tissue irritants, hi-flash solvent, or xylene.

COMMENT

Boilable Tubing Fluid.—The data from Exper. 1 and 2 shows that xylene is a potent tissue irritant and in some tissues a necrosing agent. Furthermore, xylene from the tubing fluid of boilable gut appeared to be more of an irritant to tissues than xylene (A.C.S.). This latter point raises the question as to whether the xylene used for the tubing fluid may not have been a commercial grade which contained additional irritants not present in the A.C.S. grade. Another possibility is that some irritant material from

the gut may have been extracted by the xylene which enhanced its irritant property.

It is surprising that no one has questioned the practice of using a liquid with known irritant properties as tubing fluid for surgical gut. In the experimental laboratory one of the commonest uses of xylene as an irritant is to produce vasodilation of the marginal ear vein of the rabbit in order to facilitate venepuncture. Xylene has been used to produce sterile inflammation by such students of tissue reactions as Rigdon,[2] and Hudack and McMaster.[3] Steiner[4] has used xylene in the tissues of experimental animals and found extensive tissue reactions as well as necrosis.

After a tube of boilable gut is opened it is necessary to render the gut sufficiently pliable for surgical use, because in a completely anhydrous state it is brittle and stiff. The procedure commonly recommended for accomplishing this is immersion for a few minutes in warm water or saline or wrapping it in a moist towel. Xylene is insoluble in water and the procedure designed primarily for softening the gut could not be expected to remove all the xylene. This can easily be demonstrated by the obvious smell of xylene remaining after a piece of gut has been softened in water. Manufacturers have not pointed out the desirability of eliminating the liquid which was used as a tubing fluid nor have they called attention to its irritant properties. Certainly if the xylene tubing fluid is not eliminated from boilable surgical gut before it is introduced into the tissue one should not be surprised to find in the wound a tissue reaction due in large part to the xylene left in and on the gut rather than to any inherent properties of the suture material itself.

It is customary in some operating rooms to render boilable gut pliable by immersion in 70% alcohol. This requires a longer period of time for obtaining the desired pliability than is necessary with warm water or saline, but it has the advantage of removing to a greater extent the xylene tubing fluid. Seventy per cent alcohol is not a satisfactory agent for complete removal of xylene, however, because xylene is not as freely soluble in this concentration of alcohol. Ninety-five per cent alcohol could be used but would require a longer period of time as a softening agent than can usually be afforded in the operating room and, furthermore, if one has to resort to alcohol one might just as well use nonboilable gut which is already put up in alcohol and is sufficiently pliable for immediate use when removed from the tube. An additional point regarding the use of alcohol as a softening agent and as a solvent for the xylene revolves about an observation in Exper. 3, where it was found that in certain concentrations of xylene in 95% alcohol there was apparently a greater tissue reaction observed than when either xylene or alcohol was used alone.

It is probable that some of the recently developed "wetting agents" or emulsifiers might be useful in removing the xylene from the gut. A relatively small amount of one of these in water will emulsify the xylene and favor its removal from the gut. Studies are in progress to determine what agents of

this type might be best suited to the elimination of water-insoluble irritants from surgical gut.

Although our data show that toluene is definitely less irritant and necrosing to tissues than xylene it is more of an irritant than is desirable. Furthermore, the use of toluene as a tubing fluid would subject the operating team to the hazards of inhaling toluene vapor. There has been considerable interest recently in the hazards of inhaling toluene vapor in concentrations of 50 to 200 p.p.m.* (von Oettingen, and coworkers,[5, 6] and Greenburg, and coworkers.[7]) It is not inconceivable that in a busy and not too well ventilated operating room the operating team could be exposed to a concentration of toluene vapor from the broken tubes of surgical gut sufficient to produce some of the toxic manifestations, muscle incoordination in particular, described by von Oettingen. Xylene appears to have very similar toxic properties.[8]

If manufacturers are unable to provide an anhydrous liquid for boilable surgical gut which is not only harmless to the gut, but also harmless to tissues and nontoxic when inhaled as a vapor it would appear appropriate to suggest marketing boilable products without any tubing fluid. For surgeons who are anxious to utilize suture material which is entirely free of extraneous irritants this would provide the ideal absorbable suture. It would be necessary, of course, to moisten the gut in physiologic salt solution to make it pliable.

Nonboilable Tubing Fluid.—The data from Exper. 4 and 5 show that there was a water-insoluble liquid present in varying concentrations, up to 15% by volume, in the alcoholic tubing fluid of numerous nonboilable surgical products. Neither the presence of such a liquid nor its nature was indicated on the package label where the composition of the tubing fluid is supposed to be recorded. With the cooperation of an independent laboratory this observation was further substantiated, and the water insoluble liquid identified as a high boiling range hydrocarbon mixture.

The explanation for the presence of this high boiling range water-inosluble liquid in the alcoholic tubing fluid is undoubtedly that it represents the material in which the surgical gut was heat sterilized, and this anhydrous liquid was not completely removed from the tube containing the gut before the alcoholic solution was added and the tube sealed. The striking differences in the amount of such material present in the alcoholic tubing fluids from different commercial souces (Table II) make it appear obvious that there are fundamental differences in the way various companies handle this step in the manufacture of surgical gut. Furthermore, variations were occasionally observed in this respect from tube to tube and from lot to lot in products from the same manufacturer. It is apparent from these observations that this step in the production of nonboilable surgical gut deserves considerably more attention from the manufacturers than it has received up to the present time. It is only

* Parts per million.

fair to point out here that some manufacturers have been eliminating this material from their finished products to a considerable degree. It was rather surprising to find, on the other hand, that in some products as much as 5 to 15 per cent of the alcoholic tubing fluid was in all probability the liquid which had been used in the heat sterilization process.

The presence of this material in alcoholic tubing fluids would have little practical significance were it not for its striking properties as a tissue irritant. In Exper. 8 it was shown that all the nonboilable tubing fluids were more irritant to human tissues than 95% ethyl alcohol. Furthermore, the degree of tissue reaction induced by these fluids was roughly proportional to the concentration of the water-insoluble component. It was of some interest that even traces of this material in the tubing fluid appeared to cause a more noticeable reaction than 95% alcohol. It is possible that the tissue reaction produced by products having only a trace of water-insoluble component may have been due to irritant substances extracted from the suture material by the alcohol, or to some denaturant which may have been present in the commercial grade of alcohol employed. These explanations are probably of minor significance, however, in view of the obvious necrosing action in human skin of concentrations as low as 1% in 95% ethyl alcohol (C.P.) of the pooled high boiling range distillate from alcoholic tubing fluids (Fig. 7).

The use of a petroleum derivative by at least one manufacturer, presumably to avoid using the irritant coal-tar derivatives, did not eliminate the irritant factor in the alcoholic tubing fluid because this material or at least the sample available to us was no less irritating and necrosing to tissues than hi-flash solvent.

In regard to the use of an alcoholic solution for the tubing fluid of nonboilable surgical gut it should be pointed out that 95 per cent ethyl alcohol is a tissue irritant and protein coagulant. Its irritant action in the tissues is, however, substantially less than xylene, hi-flash solvent, the petroleum derivative, and even less than toluene. Its mode of action is somewhat different as pointed out in Exper. 3 and 8. It is probable that such irritant action as may be observed in the tissues from catgut is only secondarily due to alcohol in view of the potent irritant action of the water-insoluble hydrocarbons which undoubtedly overshadows the action of the alcohol or is enhanced by it. In most operating rooms there is some lapse of time between the opening of the tube and the use of the catgut, and it is hoped that some of the alcohol has an opportunity to evaporate before the gut is introduced into the tissues. If the alcoholic tubing fluid is relatively free from water-insoluble hydrocarbon, and if the catgut is stretched out and permitted to dry or is moistened in saline, it is probable that this would represent the suture material of least extraneous irritant content which is now available.

The presence of germicidals such as potassium mercuric iodide and phenyl mercuric benzoate in the alcoholic tubing fluids offers another source of irritation, but our limited observations on this point lead us to believe it is rela-

tively insignificant in comparison with the potent irritant action of the hydrocarbon factor of tubing fluids.

The presence of appreciable quantities of a water-insoluble liquid in alcoholic tubing fluids, which was demonstrated to have an irritant action in relatively low dilutions in alcohol, and which evaporates more slowly than alcohol, could account for considerabe tissue irritation if introduced into the tissues along with surgical gut sutures.

The demonstration of a water insoluble liquid in alcoholic tubing fluid by the emulsion tests or other means does not necessarily imply that such a liquid is an irritant to tissues because some manufacturers may find a suitable anhydrous liquid for heat sterilization which is harmless to living tissues. Therefore, any residuum of such liquid in alcoholic tubing fluids would not constitute a potential source of tissue irritation if carried into the tissues along with the surgical gut.

In regard to the identity of the fluid which was found in the alcoholic tubing fluids this may be said: It has a characteristic odor; a boiling range; a solubility in water-alcohol mixtures; and a tissue irritant action which was closely similar to that observed for a hydrocarbon known as hi-flash solvent, which is believed to be the anhydrous liquid used by most manufacturers for the heat sterilization of their catgut.

SUMMARY

1. Xylene, which has been the anhydrous liquid commonly used as a tubing fluid for boilable surgical gut, was found to be a potent tissue irritant.

2. The alcoholic tubing fluids of nonboilable surgical gut were found to contain, in many instances, a water-insoluble liquid, the presence of which could be demonstrated by the addition of water which produced a white emulsion.

3. The amount of this water-insoluble liquid varied in different products, package lots, and individual tubes in the same package, from a trace to as much as 15 per cent by volume of the alcoholic tubing fluid.

4. The irritant action of the alcoholic tubing fluids were generally in excess of that observed for 95 per cent ethyl alcohol, but less than was found for xylene. The magnitude of irritant action, which in some products was rather excessive, was proportional to the amount of water-insoluble liquid in the alcoholic tubing fluid.

5. The water-insoluble liquid recovered from the alcoholic tubing fluids by emulsion separation or distillation was found to be somewhat more of a tissue irritant than xylene.

CONCLUSIONS

1. The presence of a water-insoluble liquid in alcoholic tubing fluid of nonboilable surgical gut can probably be explained on the basis that it represents a residuum of the anhydrous hydrocarbon used for the heat sterilization of the catgut, which was not eliminated from the tube before the addition of the alcoholic solution and the sealing of the tube.

2. In view of the irritant action of xylene and this water-insoluble liquid in alcoholic tubing fluids, which was probably hi-flash solvent or a similar or related anhydrous hydrocarbon, a question is raised as to whether these liquids alone or in combination with alcohol may not be carried into the tissues along with surgical gut in sufficient concentration to have an undesirable irritant action on the tissues in which the catgut is placed.

3. The use of an anhydrous liquid in the heat sterilization of catgut to obtain uniform transmission of heat without damage to the gut is conceded as a necessary step in the manufacture of surgical gut to insure the standard of sterility expected by the surgical profession. However, it would appear that general improvements could be made in some manufacturing methods from the standpoint of utilizing a liquid for heat sterilization which is nonirritating to tissues or of eliminating from tubing fluids such hydrocarbons as have been found to have irritant properties to living tissues.

REFERENCES

[1] Jenkins, H. P., and Hrdina, L. S.: Absorption of Surgical Gut: I—The Decline in Tensile Strength in the Tissues, Arch. Surg., **44**, 881, May, 1942: II—Pepsin Digestion Tests for Evaluation of Duration of Tensile Strength in the Tissues, Arch. Surg., **44**, 984, June, 1942. Jenkins, H. P., Hrdina, L. S., Owens, F. M., and Swisher, F. M.: Absorption of Surgical Gut: III—Duration in the Tissues after Loss of Tensile Strength, Arch. Surg., **45**, 74, July, 1942. Jenkins, H. P.: Absorption of Surgical Gut: IV—Recommendations for Absorbability and Digestibility Specifications. Arch. Surg., **45**, August, 1942.

[2] Rigdon, R. H.: Capillary Permeability in the Skin of the Rabbit, Proc. Soc. Exper. Biol. & Med., **42**, 43, 1930.

[3] Hudack, S. S., and McMaster, P. D.: The Breakdown of Lymph Transport, Proc. Soc. Exper. Biol. & Med., **28**, 853, 1931.

[4] Steiner, Paul E.: Fatal Pseudo-anaphylaxis by Intramuscular Injection of Benzene and Related Substances. J. Immunology, **27**, 525, December, 1934.

[5] Von Oettingen, W. F., Neal, P. A., Donahue, D. D., Svirbely, J. L., Baernstein, H. D., Monaco, A. R., Valaer, P. J., and Mitchell, J. L.: The Toxicity and Potential Dangers of Toluene; With Special Reference to its Maximal Permissible Concentration. U. S. Public Health Service, Public Health Bulletin No. 279, 1942.

[6] Von Oettingen, W. F., Neal, P. W., and Donahue, D. D.: The Toxicity and Potential Dangers of Toluene. J. A. M. A., **118**, 579, February, 1942.

[7] Greenburg, Leonard, Mayers, May R., Heimann, Harry, and Moskowitz, Samuel: The Effects of Exposure to Toluene in Industry. J. A. M. A., **118**, 573, February, 1942.

[8] Jacobs, M. B.: Analytical Chemistry of Industrial Poisons, Hazards and Solvents. Interscience Publishers Inc., New York, 1941.

HYDROCARBON CONTENT OF NONBOILABLE SURGICAL GUT TUBING FLUIDS*

ALBERT E. SIDWELL, JR., PH.D.

CHICAGO, ILL.

FROM THE CHEMICAL LABORATORY, AMERICAN MEDICAL ASSOCIATION, CHICAGO, ILL.

CURRENTLY MARKETED nonboilable surgical gut is packaged in sealed glass tubes, scored for breaking at the midpoint. Each tube contains a single strand of surgical gut with or without a spool, a loose paper label insert, and a quantity of clear fluid known as "tubing fluid." According to requirements of the United States Pharmacopeia, the composition of the tubing fluid used in packaging surgical gut must be stated in the labeling of market packages of the product,

In the course of a study of tissue irritation associated with the tubing fluids employed in marketing surgical gut, Drs. H. P. Jenkins and C. L. Dunham, of the University of Chicago, observed that the admixture of water with the tubing fluids from some brands of nonboilable surgical gut produced white emulsions of varying turbidity. These investigators found that the emulsions thus formed broke on standing, with the formation of water-immiscible, supernatant liquid layers of varying volume. These findings were brought to the attention of the A. M. A. Chemical Laboratory. Because of the possible serious implications, an independent chemical examination was made of the tubing fluids used in packaging nonboilable surgical gut marketed by various manufacturers. For this purpose, original market packages of size one, nonboilable, sterile surgical gut of both plain and medium chromic types, representative of the products of nine different manufacturers, were purchased on the open market for examination.

According to statements found on the package labels, the tubing fluids used in the products obtained may be classified as follows:

(a) 95 per cent ethyl alcohol containing varying amounts (0.1 to 0.3 per cent) of potassium mercuric iodide.
(b) 76 per cent ethyl alcohol, 20 per cent isopropyl alcohol and phenylmercuric benzoate 0.025 per cent in water.
(c) 95 per cent ethyl alcohol containing phenylmercuric benzoate 0.02 per cent.
(d) Anhydrous ethyl alcohol containing 10 per cent methanol.
(e) 97 per cent ethyl alcohol containing phenylmercuric nitrate 0.025 per cent.

It is apparent that this classification includes no water-insoluble liquid constituents. However, the results of this investigation indicate the presence of up to 14 per cent (V/V) of water-insoluble liquid aromatic hydrocarbons in some of the nonboilable surgical gut "tubing fluids" examined. The physical and chemical properties of the water-insoluble materials isolated from various specimens lead to the conclusion that the tubing fluid contains mate-

* Read by title before the American Surgical Association, May 13–14, 1943, Cincinnati, Ohio.

rial closely related to a coal-tar distillate, the so-called "xylene fraction" or solvent naphtha. Specimens of the hydrocarbons isolated from nonboilable tubing fluids in this laboratory were submitted to Doctors Jenkins and Dunham.[1] Injection of these materials, when administered either undiluted or in the form of alcoholic solutions, produced tissue irritation.

TABLE I

AROMATIC HYDROCARBON CONTENT OF SURGICAL GUT TUBING FLUID

Manufacturer*	Gut Type	Odor Test	Per Cent Hydrocarbon Found (V/V)	Principal Boiling Range of Isolated Hydrocarbons
1	A	+	2.5	167°-170° C.
	C	+	4.8	
2	A	+	1.9	172°-174° C.
	C	+	0.7	
3	A	—	0.4	
	C	—	0.03	
4	A	+	3.3	152°-174° C.
	C	+	2.6	
5	A	—	0.02	154°-158° C.
	C	+	5.9	
6	A	—	0.15	
	C	—	0.10	
7	A	—	0.05	
	C	—	0.05	
8	A	+	14.0	152°-174° C.
	C	+	6.8	
9	A	+	1.4	
	C	+	0.6	

*The method of indicating manufacturer by the numbers 1, 2, 3, etc., does not represent the same code as that used by Jenkins and Dunham.

EXPERIMENTAL STUDIES

Original market packages of size one, nonboilable surgical gut (U.S.P.), of both Type A (plain) and Type C (medium chromic) were purchased from a surgical supply house. The products of nine different manufacturers were obtained. The fluids found in individual tubes served as specimens for study.

A. *Odor:* The odor of the tubing fluid contained in individual tubes was used as a rough index of the presence or absence of aromatic hydrocarbons. It was found that tubing fluids, later shown to contain less than 0.4 per cent (V/V) of aromatic hydrocarbons yielded only the odor of the alcohols present. Positive results obtained by the odor test are shown in Table I by plus (+) signs.

B. *Composite Distillate:* Tubing fluids whose odors indicated the presence of aromatic hydrocarbons were pooled and mixed with ten volumes of water. Sufficient normal sodium hydroxide to render the emulsion alkaline was added and the mixture was distilled. The initial portion of the distillate was cloudy emulsion. The distillation was continued until only a single fluid was discharged from the condenser. The collected distillate was treated with two volumes of water, acidified with diluted sulfuric acid, and distilled again, until only a single fluid was discharged from the condenser. The final distillate was treated with two volumes of water and allowed to stand in a stoppered

graduated cylinder until the white emulsion broke and a clear supernatant liquid layer formed. The liquids were separated and the water-insoluble material was dried with anhydrous sodium sulfate. On distillation, the boiling point range of this material was found to be from 140° to 190° C. The total distillate was divided into two portions. One portion was submitted to Doctors Jenkins and Dunham for tissue irritation studies; the other was retained for chemical examination. The isolated fluid burned in air with a yellow, smoky flame. One volume of the liquid was found to be soluble in three volumes of fuming sulfuric acid. Qualitative tests indicated the absence of halogens, nitrogen and sulfur. The refractive index of the liquid was found to be 1.49 at 25° C., and the specific gravity found was 0.861 at 25° C. It was soluble in ethyl alcohol, methyl alcohol and isopropyl alcohol, but insoluble in water. Traces of the material yielded a reddish-brown color with concentrated sulfuric acid containing small amounts of formaldehyde.

C. *Individual Tubing Fluids:* Material isolated, as described in (B), was used as a control substance, dissolved in alcohol, in the further investigation of individual tubing fluids. An adaptation of the British[2] standardized test for benzene in air was applied to individual tubing fluids in appropriate ethyl alcohol dilution. The prepared solutions were transferred to an apparatus designed to allow aspiration of a measured volume of air through the unknown solution and thence through a known volume of a reagent consisting of five cubic centimeters of 40 per cent formaldehyde solution per 100 cc. of concentrated sulfuric acid. Spectrophotometric measurements at 500, 550 and 600 m. on the colored solutions obtained indicated the presence of up to 14.0 per cent (V/V) of aromatic hydrocarbons in the various original tubing fluids studied. The results are shown in Table I.

D. *Hydrocarbons from Individual Tubing Fluids:* Specimens of tubing fluid from individual products found by test to contain aromatic hydrocarbons were distilled from aqueous solutions as described under (B), and portions of the hydrocarbons obtained were submitted to Doctors Jenkins and Dunham for tissue irritation studies. The isolated materials were found to be completely soluble in fuming sulfuric acid and responded to tests for aromatic hydrocarbons. The boiling points found are shown in Table I.

SUMMARY

Chemical examination of marketed specimens of nonboilable surgical gut (U.S.P.), representing products of nine different manufacturers, indicated the presence of up to 14.0 per cent (V/V) of high boiling aromatic hydrocarbons in the tubing fluids. These hydrocarbons are related to a coal-tar distillate known as the "xylene fraction" or solvent naphtha.

REFERENCES

[1] Dunham, C. L., and Jenkins, H. P.: Surgical Gut (Catgut) Tubing Fluid as a Tissue Irritant. ANNALS OF SURGERY, **118**, 269, August, 1943.

[2] Dept. Sci. Ind. Research, Brit., Leaflet No. 4, 1939. Cited by Jacobs, M .B.: Analytical Chemistry of Industrial Poisons, Hazards and Solvents, P. 402, Interscience Publishers, Inc., 1941.

IRRITANT PROPERTIES OF TUBING FLUIDS AS A FACTOR IN THE TISSUE REACTIONS OBSERVED WITH SURGICAL GUT (CATGUT)*

HILGER PERRY JENKINS, M.D., AND CHARLES LITTLE DUNHAM, M.D.
CHICAGO, ILL.

FROM THE DEPARTMENT OF SURGERY AND THE DEPARTMENT OF MEDICINE, UNIVERSITY OF CHICAGO, SCHOOL OF MEDICINE, CHICAGO, ILL.

In the previously reported work on the "Absorption of Surgical Gut (Catgut[1])" it was pointed out in the discussion of the possible explanations of the tissue irritation which frequently was associated with the experimental catgut implants that this may have been due to irritants in the tubing fluid such as the xylene of boilable products, the alcohol of nonboilable products, or the water-insoluble liquid which was found to be present in some nonboilable alcoholic tubing fluids. The surgical gut tubing fluids were made the subject of further study to clarify this point, and preliminary reports of this work have already appeared.[2]

In the preceding communication by Dunham and Jenkins[3] it was found that the surgical gut tubing fluids were tissue irritants of varying degree depending on the composition of the fluid. The irritant properties were evaluated by the intradermal injection of 0.05 cc. amounts of the various fluids into the skin of dogs and human subjects and observing the lesions produced thereby. The boilable variety of surgical gut tubing fluid, which was xylene, was found to be especially damaging to tissues. The nonboilable variety of tubing fluids which were recorded on the package label as consisting of various alcoholic solutions containing a fraction of one per cent of a germicidal agent, was somewhat less damaging to tissues than the xylene tubing fluid, however, the magnitude of the tissue reaction was frequently considerably in excess of that obtained by 95 per cent ethyl alcohol. This excessive irritant action of a considerable proportion of the alcoholic tubing fluids as compared with 95 per cent ethyl alcohol was apparently due to the presence of a water-insoluble liquid in the alcoholic tubing fluids. The amount of this liquid varied from a trace to as much as 15 per cent by volume in the various products tested. The presence of this water-insoluble liquid in the nonboilable surgical gut tubing fluids was further corroborated by Sidwell,[4] and identified as a high boiling range aromatic hydrocarbon mixture related to a coal-tar distillate known as "xylene fraction" or solvent naphtha.

The presence of this water-insoluble liquid in the alcoholic tubing fluids of nonboilable surgical gut undoubtedly represented a residue of the anhydrous liquid which was used by the manufacturer for the heat sterilization of the catgut and which was not eliminated from the tube of catgut before the

*Read by title before the American Surgical Association, May 13-14, 1943, Cincinnati, Ohio.

alcoholic solution was added and the tube sealed. This liquid was found to be somewhat more damaging to tissues than xylene and its irritant action could be detected in relatively low dilutions in 95 per cent ethyl alcohol. A sample of the liquid which was believed to be the anhydrous hydrocarbon used by most of the surgical gut manufacturers, and which has been known as hi-flash solvent, was found from the standpoint of tissue irritation, solubility in water-alcohol mixtures, and boiling range to have properties similar to the water-insoluble liquid which was recovered from most of the alcoholic tubing fluids.

The practical significance of these observations on the irritant properties of surgical gut tubing fluids depends upon whether the tubing fluids are carried into the tissues along with the catgut in sufficient concentration to have an irritant action on the tissues in which the catgut is embedded.

In an endeavor to evaluate this point a number of experiments were devised: 1. Weighings were made of catgut to determine the amount of tubing fluid which remained on or in the catgut strand after removal from the tube. 2. Intradermal injection tests were carried out on dogs and patients utilizing amounts and concentrations of xylene or hi-flash solvent which were comparable to that found in the catgut by the weighing experiments. 3. Implantations of catgut in the tissues were made with and without washing procedures designed to eliminate tubing fluid irritants.

EXPERIMENTAL STUDIES

1. Weighing Tests.—*Boilable Catgut:* Standard tubes of boilable catgut, which contained xylene as the tubing fluid according to the package label, were opened, the catgut was wiped with a dry cloth and then weighed, utilizing a glass-encased high sensitivity scale (sensitive to 0.1 mg.). The catgut was then placed in a vacuum desiccator and removed for subsequent weighings until such time as a constant weight was obtained.

	Weight	Loss of Weight	Concentration of Volatile Material
	NO. 2 SIZE OF TYPE A—PLAIN SURGICAL GUT		
Original	0.3612 Gm.		
40 minutes	0.3585 Gm.	2.7 mg.	
3 hours	0.3565 Gm.	4.7 mg.	
20 hours	0.3561 Gm.	5.1 mg.	1.4%
	NO. 2 SIZE OF TYPE A—PLAIN SURGICAL GUT		
Original	.3975 Gm.		
35 minutes	.3944 Gm.	3.1 mg.	
3 hours	.3925 Gm.	5.0 mg.	
20 hours	.3925 Gm.	5.0 mg.	
7 days	.3924 Gm.	5.1 mg.	1.28%
	NO. 2 SIZE OF TYPE C—MEDIUM CHROMIC SURGICAL GUT		
Original	0.3128 Gm.		
35 minutes	0.3117 Gm.	1.1 mg.	
3 hours	0.3074 Gm.	5.4 mg.	
20 hours	0.3070 Gm.	5.8 mg.	
5 days	0.3052 Gm.	7.6 mg.	2%
	NO. 1 SIZE OF TYPE A—PLAIN SURGICAL GUT		
Original	0.3970 Gm.		
45 minutes	0.3924 Gm.	4.6 mg.	
3 hours	0.3912 Gm.	5.8 mg.	
24 hours	0.3898 Gm.	7.2 mg.	
48 hours	0.3893 Gm.	7.7 mg.	1.9%

To determine the adequacy of the wiping procedure to eliminate the xylene on the surface of the gut additional tests were carried out in which the surface xylene was eliminated by subjecting the gut to a preliminary ten-minute period of vacuum desiccation as soon as it was removed from the tube. This period of time was apparently adequate for the elimination of the xylene on the surface of the gut.

NO. 2 SIZE OF TYPE C—MEDIUM CHROMIC SURGICAL GUT

	Weight	Loss of Weight	Concentration of Volatile Material
Original	0.3556 Gm.		
10 minutes	0.3442 Gm.	11.4 mg.	3.2%
1½ hours	0.3427 Gm.	1.5 mg.	
20 hours	0.3390 Gm.	5.2 mg.	1.5%
3 days	0.3374 Gm.	6.8 mg.	1.9%

It would appear from these observations that practically all of the surface xylene was eliminated from the gut by the initial vacuum treatment, in view of the fact that in the next hour and one-half only 1.5 mg. were eliminated. It should be of particular interest that the most substantial portion of the residual xylene was not recovered until the following day. The residual concentration of volatile material of 1.9 per cent after elimination of surface xylene compares favorably with the results obtained by wiping the gut before obtaining the original weight.

These observations establish the fact that one to two per cent by weight of the larger sizes of boilable catgut consists of volatile material which appears to be within the strand of gut rather than on its surface. The relatively long periods of time required to eliminate this volatile material from the gut by vacuum desiccation is a point of considerable importance. Boilable gut must be prepared in a strictly anhydrous condition and, if this amount of weight loss were due to water in the gut, it is very probable that the heat sterilization process would have seriously damaged the gut, which is quite vulnerable to heat in the presence of any appreciable amount of moisture. Therefore, the one to two per cent loss of weight which was found after elimination of surface xylene was presumed to represent the concentration of xylene within the strand of catgut and which was eliminated only by prolonged treatment in the vacuum desiccator. It is very improbable that this would be eliminated by the operating room procedures customarily utilized for inducing pliability of the gut before its use in the tissues, such as dipping in water, saline, or 70 per cent alcohol for a few minutes.

Nonboilable Catgut: Standard tubes of nonboilable surgical gut which contained alcoholic tubing fluid and a germicidal agent, according to the package label, were opened, the frame supporting the gut was removed, and the strand weighed immediately. Then the strand was stretched out, as is customarily done in the operating room as soon as it is removed from the tube and weighed again.

Following this, the strand was placed in the vacuum desiccator and re-

moved from time to time for subsequent weighings. The original weight used for computing the ultimate loss of weight was the reading taken after stretching out the catgut, as this is more nearly representative of the condition of the gut when it is used in the operating room.

NO. 2 TYPE A—PLAIN SURGICAL GUT (5% HYDROCARBON IN ALCOHOLIC TUBING FLUID)

	Weight	Loss of Weight	Significant Concentration of Volatile Material (Alcoholic Tubing Fluid)
Original	0.6240 Gm.		
After stretching	0.5820 Gm.	42.0 mg.	
1 hour	0.5204 Gm.	61.6 mg.	
20 hours	0.4840 Gm.	98.0 mg.	16.8%
3 days	0.4728 Gm.	109.2 mg.	18.7%

NO. 2 TYPE C—MEDIUM CHROMIC SURGICAL GUT (2% HYDROCARBON IN ALCOHOLIC TUBING FLUID)

Original	0.5704 Gm.		
After stretching	0.5348 Gm.	35.6 mg.	
1 hour	0.4717 Gm.	63.1 mg.	
20 hours	0.4403 Gm.	94.5 mg.	17.6%
3 days	0.4302 Gm.	104.6 mg.	19.3%

NO. 1 TYPE A—PLAIN SURGICAL CUT (5½% HYDROCARBON IN ALCOHOLIC TUBING FLUID)

Original	0.5050 Gm.		
After stretching	0.4830 Gm.	22.0 mg.	
1 hour	0.4297 Gm.	55.3 mg.	
20 hours	0.4000 Gm.	83.0 mg.	17%
3 days	0.3907 Gm.	92.3 mg.	19.3%

NO. 1 TYPE C—MEDIUM CHROMIC SURGICAL GUT

Original	0.3600 Gm.		
After stretching	0.3520 Gm.	8.0 mg.	
1 hour	0.3128 Gm.	39.2 mg.	
20 hours	0.2946 Gm.	57.4 mg.	16.2%
3 days	0.2887 Gm.	63.3 mg.	17.9%

These observations establish the fact that as much as 18 per cent by weight of the larger sizes of nonboilable surgical gut may be composed of volatile material when it is used in the operating room as soon as it is removed from the tube and stretched out according to directions of the manufacturer. If the catgut is not stretched out before it is used it may have as much as 22 per cent by weight of volatile material in or on the catgut. The volatile component of the surgical gut is presumably the alcoholic tubing fluid which, in this instance, was recorded on the package label as 96 per cent alcohol but which also was found to contain appreciable quantities of a water-insoluble liquid which is believed to be hi-flash solvent. Thus, we have three components to consider, the alcohol, the water, and the hi-flash solvent (B.P.) 163°-180° C. In view of the rather striking differences in the boiling points of these three liquids it would not be surprising to find some selectivity in their elimination from the gut in the vacuum desiccator. The presence of 18 per cent alcohol by weight, of course, would mean a considerably higher concentration if estimated from the standpoint of volume in view of the low specific gravity of alcohol. Thus, we have to consider that at least 20 per cent by volume of the catgut is volatile material. With this point estab-

lished we must also take into consideration that there may be from five per cent to ten per cent of hi-flash solvent in some of the alcoholic tubing fluids. Surgical gut which is put up in such a tubing fluid would then be expected to have at least a concentration of one to two per cent by volume, or 0.9 per cent to 1.8 per cent by weight of hi-flash solvent in the gut.

Aside from the relative concentration of xylene or hi-flash solvent, which may be as much as one to two per cent in the catgut, one should take into consideration the actual amount present in the length of catgut which is required for a single ligature. It requires approximately 3 cm. of a No. 1-size catgut for an ordinary ligature if a triple throw knot is used and the ends of the strand cut within two to three millimeters of the knot. There are approximately 150 cm. of catgut in a standard strand. Therefore, if one has as much as five milligrams, or more, of xylene present in the entire strand one would have at least 0.1 mg. in three centimeters of catgut concentrated in a relatively small focal point. Similar analogies obtain in regard to hi-flash solvent if it is present in five to ten per cent concentrations in the alcoholic tubing fluid. Subsequent intradermal injection experiments will demonstrate the effect of this amount of material in the tissues. In regard to the alcohol in the nonboilable catgut there may be as much as 1.5 mg. of alcohol in a single ligature of No. 1 catgut, aside from any hi-flash solvent component.

These tests demonstrate that it requires an hour of vacuum dessication to eliminate 60 per cent of the volatile material in nonboilable surgical gut, which would appear to be alcohol, water, and a trace to as much as 15 per cent of a high boiling point hydrocarbon. Therefore, it is improbable that more than half of the tubing fluid would be eliminated by evaporation during the course of an ordinary operation if the gut was removed from the tubes at the beginning of the operation. Furthermore, it is likely that the material with the high boiling range would remain in the gut longer than the alcohol. Whatever tubing fluid that fails to be eliminated by evaporation would obviously be carried into the tissues along with the suture.

2. Intradermal Injection Experiments.—To ascertain the action on the tissues of relatively minute amounts of the water-insoluble hydrocarbons, xylene and hi-flash solvent, they were made up in varying concentrations as an emulsion in physiologic saline solution, with the aid of an emulsifying agent such as Ninol 737 or Atlas Tween 20. Intradermal injections of 0.05 cc. amounts were made in the skin of dogs and patients and the resulting lesions observed:

In the series of injection experiments on animals, 10 per cent, 5 per cent, 1 per cent, and 0.5 per cent emulsions of xylene and hi-flash solvent in saline were used. The concentration of emulsifying agent (Ninol 737) in the 10 per cent emulsion was 2 per cent, in the 1 per cent emulsion 0.2 per cent. In addition, 10 per cent, 5 per cent and 1 per cent dilutions of concentrated HNO_3 were used for comparison. The results of these tests showed that the 10 per cent and 5 per cent emulsions of xylene or hi-flash solvent were capable of producing necrosis of the skin whereas the 1 per cent and 0.5 per cent

emulsions produced small inflammatory lesions which subsided after several days without producing necrosis. The emulsifying agent alone in the 2 per cent concentration produced a small nonnecrosing inflammatory lesion, but in 0.5 per cent to 0.2 per cent concentrations the lesion produced was practically negligible. The 10 per cent and 5 per cent nitric acid solution produced skin necrosis which was somewhat less conspicuous than was observed for the 10 per cent and 5 per cent emulsions, but in the 1 per cent HNO_3 concentration the lesion was somewhat more noticeable than the 1 per cent emulsion preparations, but did not go on to necrosis.

In another series of animals 5 cc. of Evans blue (T-1824) was injected intravenously before the intradermal injections were made. It was of considerable interest to observe that emulsion preparations as well as the dilutions of HNO_3 produced a blue discoloration of the skin at the site of injection which was noticeable within a few minutes and spread to an area of 1-2 cm. about the site of injection. This would appear to indicate that a fairly rapid damaging effect of the capillaries is obtained with loss of plasma at the point of injection. Some blue discoloration occurred for the 2 per cent Ninol as well as for distilled water which was also used in this series as a control. The distilled water injection produced a temporary lesion which did not go on to necrosis. No noticeable blue color was found at the site of injection of the saline controls or the 0.5 per cent or 0.2 per cent emulsifying agent (Ninol).

In the intradermal skin tests on patients 1 per cent, 0.5 per cent, 0.1 per cent and 0.05 per cent emulsions of xylene or hi-flash solvent in physiological saline were used in 0.05 cc. or 0.025 cc. amounts. Ninol in 0.2 per cent concentration was used for some of the 1 per cent emulsions, whereas Atlas Tween 20 was used in most of the tests in 0.5 per cent concentration in the 1 per cent emulsions. The more dilute emulsions contained proportionately less emulsifying agent, that is the 0.1 per cent emulsion contained only 0.05 per cent of emulsifying agent. Sixteen patients were subjected to injection tests, the results of which showed that the 1 per cent emulsions of xylene or hi-flash solvent rather consistently produced a small inflammatory lesion at least 1 cm. in diameter which could be detected up to one to three weeks after injection as a small area of induration or redness. The injection produced considerable pain. The 0.5 per cent emulsions produced similar but slightly less conspicuous lesions. The 0.1 per cent emulsions produced a noticeable inflammatory lesion which generally lasted for one to three days or sometimes longer, although in some instances these were difficult to detect after 24 hours. The 0.05 per cent emulsion injections produced relatively transient lesions which were difficult to identify after 24 hours, although in one patient the lesion could be detected for two days after the injection. The controls of 0.5 per cent Tween 20 in saline produced transient lesions which were relatively minimal in comparison with the 1 per cent emulsions with which they were compared. The saline controls did not produce any persistent detectable lesions. Distilled water controls produced a transient lesion

which was painful at the time of injection. There was a slight pain sensation associated with the 0.5 per cent Tween 20 controls, and slightly more pain with the 0.1 per cent emulsions. There was no noticeable difference in the effect of the xylene as compared with hi-flash solvent in comparable dilutions in the same patient.

To compare the weighing experiments mentioned above with the amount of xylene or hi-flash solvent used in the intradermal tests the following table is presented which gives the amount of hydrocarbon in cubic centimeters and milligrams which is present in the 0.05 cc. of emulsion which was used for injection purposes:

1%	0.5%	0.1%	0.05%
0.0005 cc.	0.00025 cc.	0.00005 cc.	0.000025 cc.
5/10,000 cc.	25/100,000 cc.	5/100,000 cc.	25/1,000,000 cc.
0.43 mg.	0.215 mg.	0.043 mg.	0.0215 mg.

In the weighing experiments it was found that 3 cm. of No. 1 catgut could contain as much as 0.1 mg. of xylene or a similar amount of hi-flash solvent if the concentration of this was 5 per cent or more in the alcoholic tubing fluid which was not at all uncommon in many nonboilable products. Therefore, the amount of irritant hydrocarbon which may be present in a single ligature of No. 1 catgut is approximately midway between the hydrocarbon content of the 0.5 per cent and the 0.1 per cent emulsion injections. In view of the fact that these concentrations of hydrocarbon will produce evidence of inflammatory reaction in the tissues of patients which were subjected to test it is reasonable to presume that the hydrocarbon content of a single ligature is capable of producing an inflammatory reaction about the catgut.

In four patients it was possible to obtain a microscopic section of the lesions produced by the injection tests. The tissue was obtained by operation, such as amputation or excision of a tumor or scar requiring removal of adjacent normal skin, or by punch biopsy. In three of these sections which were made through lesions produced by 1 per cent or 0.5 per cent emulsions of hi-flash solvent there was a definite polymorphonuclear leukocytic invasion of the tissues which was limited to the area of injection. In the punch biopsy of the lesion produced by 0.1 per cent emulsion the leukocytic invasion was less marked (Fig. 1).

3. Surgical Implants in the Tissues: A series of dogs were subjected to implantation tests using as many as six different standard products. Some of the implantations were done with boilable gut and others with nonboilable gut. The animals were operated upon under ether anesthesia, and the implantations made in the abdominal muscles under aseptic technic, as described in the previously reported work on "Absorption of Surgical Gut." The boilable variety of catgut was implanted direct from the tube, after dipping in 70 per cent alcohol or saline long enough to induce pliability, after prolonged washing in 95 per cent alcohol, and after subsequent washing in saline. Non-

boilable products were implanted after removal from the tubes, and after prolonged washing in alcohol.

The results of these tests showed that in boilable products there was tissue irritation about the catgut implant which was manifest grossly as exudate and microscopically as an intense polymorphonuclear leukocytic invasion of the surrounding tissues, unless rather prolonged washing in 95 per cent ethyl alcohol had been previously carried out and the catgut dried or subsequently washed in saline. Even this procedure did not eliminate evidence of irrita-

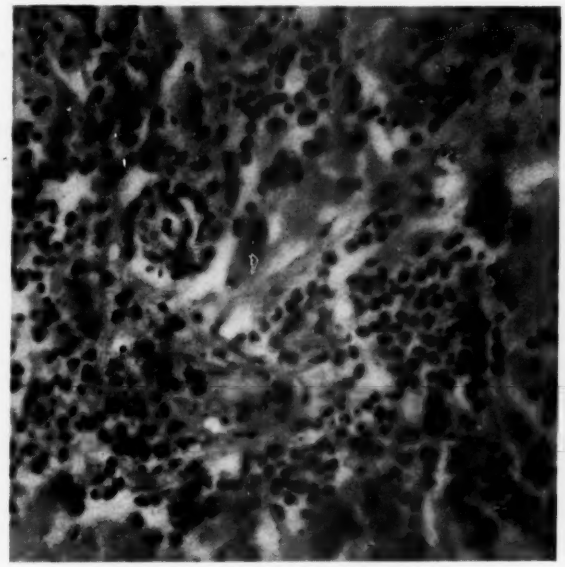


FIG. 1.—Showing cellular response 24 hours after the injection of 0.5% emulsion of tubing fluid hydrocarbon in patient. This represents 0.215 mg. of hydrocarbon. The rather striking polymorphonuclear leukocytic invasion of the tissues at the site of injection is an index to the irritant property of such liquids. At least this amount of hydrocarbon may be present in the length of gut required for two ligatures of No. 1 size of catgut if the original tubing fluid were xylene or an alcoholic solution containing 5% or more of a similar hydrocarbon, and prepared for surgical use by ordinary operating room technics.

tion in many instances, although it did tend to minimize it. Dipping the catgut in water or 70 per cent alcohol for a period of time which is adequate to induce pliability such as is the custom in operating rooms where boilable products are used did not appear to eliminate to any appreciable extent the evidence of tissue irritation (Fig. 2).

Another point which deserves mention is that in a number of instances where boilable products were implanted on one side of the abdominal wall of dogs and nonboilable products which were relatively free from hydrocarbons on the opposite side, it was found that a rather striking difference could be observed on the two sides from the standpoint of extensive edema of the abdominal wall where the boilable products had been implanted. Xylene is capable of producing edema of this magnitude in the tissues.

In the nonboilable products the washing in 95 per cent ethyl alcohol for a day or more and subsequent drying usually resulted in the elimination of gross evidence of tissue reaction such as exudate; however, there was microscopic evidence of polymorphonuclear invasion about certain products which

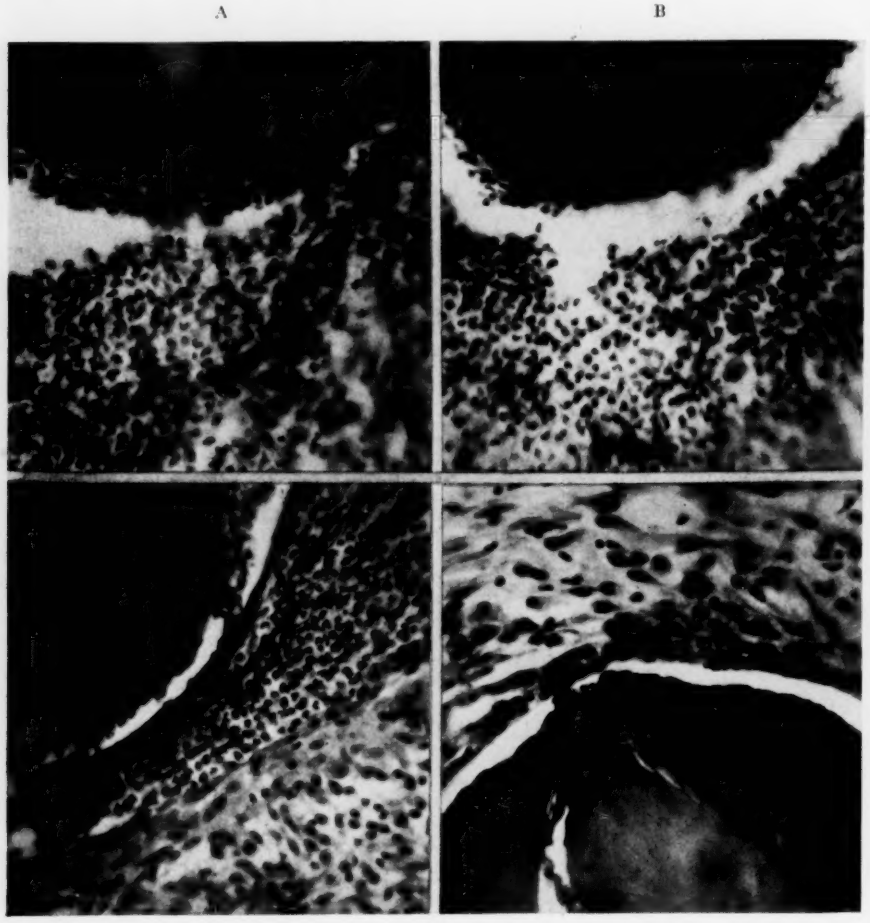
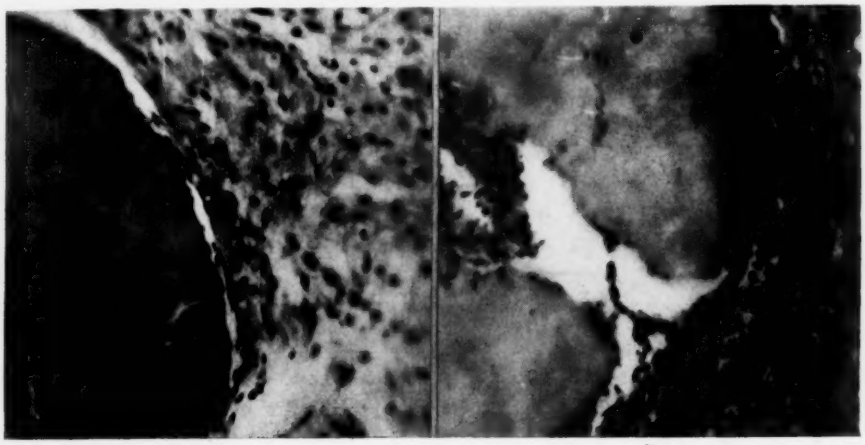


FIG. 2.—Showing tissue response to portions of the same strand of No. 000-size of Type C medium chromic boilable surgical gut, after ten days in the tissues of the same animal. A. Implanted direct from xylene tubing fluid and showing excessive polymorphonuclear leukocytic invasion of the tissues about the gut. B. Implanted after dipping in 70% alcohol long enough to induce pliability and showing conspicuous leukocytic response. C. Implanted after dipping in water long enough to induce pliability and showing leukocytic response. D. Implanted after washing in 95% ethyl alcohol for 24 hours and subsequent washing in saline for six hours, and showing practically no leukocytic response, only fibroblasts and macrophages. This represents as minimal amount of tissue reaction as could be obtained with any type of suture material.

were generally those which had the most hydrocarbon in the original alcoholic tubing fluid. The catgut which gave the least evidence of irritation as evidenced by minimal leukocytic response was usually that which was relatively free from hydrocarbon in the alcoholic tubing fluid (Fig. 3). In comparing these observations with previous implants, which were done in the course of

the work on the Absorption of Surgical Gut, it was quite obvious that the excessive exudate which characterized certain products was substantially reduced by washing in 95 per cent ethyl alcohol as compared with what was usually previously observed. Furthermore, it was observed that unless the alcoholic solution was permitted to evaporate to some extent before implanting the catgut one may have evidence of appreciable irritation in the tissues without the presence of any hydrocarbon in the alcoholic solution. This is not surprising in view of the known irritant action of alcohol, which was further demonstrated in previous injection experiments.



A B

FIG. 3.—Showing contrast in tissue response to No. 000-size of Type C—medium chromic surgical gut, which was subjected to the washing procedure in 95% ethyl alcohol and subsequent drying before being implanted in the same animal. A. Product which was relatively free from hydrocarbon in the original tubing fluid and which did not elicit any appreciable polymorphonuclear leukocytic response. The macrophage, fibroblast, and lymphocytic response shown is the characteristic tissue response to relatively inert foreign material. B. Product which had 5%, or more, of hydrocarbon in the alcoholic tubing fluid which was apparently not entirely eliminated by the washing procedure, in view of the noticeable polymorphonuclear leukocytic invasion about, and even within, the catgut which is evidence of tissue irritation. (Digestion time in pepsin or trypsin of these two products were to a considerable extent comparable.)

The main point brought out in these implantation tests is that the irritating effect of the hydrocarbon in the gut may be substantially reduced in most instances by washing the suture in 95 per cent ethyl alcohol for 24 hours and subsequently eliminating the alcohol by evaporation or washing in saline. This procedure is not recommended for clinical use because of the possibility of introducing a factor of bacterial contamination of the suture.

COMMENT

In reviewing the literature on suture material and wound healing, one finds a considerable number of articles which deal with the superiority of silk, cotton, or stainless steel wire over catgut as ligature or suture material. These reports deal with clinical and experimental studies in which the authors found that wounds closed with catgut had more evidence of tissue reaction, as evidenced by redness, induration or serum formation, were more susceptible to infections, or were less secure than wounds closed with silk, cotton, or stainless steel wire.

Considerable interest in critical analyses of the healing of surgical wounds has been stimulated by the work of Whipple, Meleney, Harvey, Howes, and others. This has contributed substantially to improved technic and generally better wound healing in surgical cases.

In Whipple's[5] report on the use of silk in the repair of clean wounds, he pointed out that there was a far larger zone of leukocytes about catgut implants in the abdominal wall of the rat than about silk, which appeared to indicate a more irritative reaction of the tissues to catgut than to silk. Meleney[6] found that in experimental observations on dogs that catgut wounds contained more bacteria than silk wounds, and, on the basis of this and a very extensive critical analysis of the incidence of infections and other complications in wounds closed with catgut or silk, concluded that the use of catgut favored the growth of organisms introduced at the time of operation.

Guthrie,[7] in a clinical report on 470 surgical operations with silk technic, was convinced that silk had advantages over catgut because wounds healed with less tissue reaction, serum pockets seldom formed, and infections occurred less often in silk than in catgut wounds. Puestow,[8] in a series of 100 thyroidectomies closed with catgut as compared with an equal number closed with silk, found that an advantage of the silk was a lower incidence of infection and serum drainage and better scars. Shambaugh,[9] in his review of wound complications following herniotomy, found that the incidence of suppurative wound infections in the catgut series was twice that in the silk series. Also he found that minor wound complications such as hematoma or accumulation of serum were eight times as frequent in the catgut series as in the silk group.

Shambaugh and Dunphy,[10] in their experimental studies on dogs, showed that operative wounds repaired with silk tolerate bacterial contamination better than similar wounds repaired with catgut. Cutler and Dunphy[11] reported on clinical and experimental observations on the use of silk in contaminated wounds and concluded that silk could be used in the presence of infection, and that the degree of infection in the immediate postoperative course was less than when catgut was used. Dunphy and Botsford,[12] in their report of a study of 600 thyroidectomies closed with silk or catgut, found that the incidence of nonsuppurative wound complications, such as induration or serum formation, as well as suppurative complications, was substantially reduced in the silk series as compared with catgut, even when it was used by meticulous technic.

In the work of Meade and Ochsner,[13] which has stimulated the use of cotton suture material in many places, it was found that catgut produced the most reaction in the tissues and the slowest healing as compared with linen, silk, or cotton, the latter appearing to produce the least reaction and the earliest healing.

Babcock's[14] reports on the use of alloy steel wire for ligatures and sutures has been responsible for the use of this material in a number of surgical clinics. In his observations on wounds closed with catgut as compared with

alloy steel wire, he felt that catgut produced reactions which retarded healing and favored infection. One observation which was made, which is quite pertinent, is that in testing catgut by implanting it in the skin he reported that this caused a red flare and a wheal in 24 hours which progressed up to a week, so that there was a zone of reaction and necrosis about each strand. This reaction is identical to that which was observed for xylene or hi-flash solvent when injected into the skin. Other favorable reports on stainless steel wire have been made by Preston,[15] and by Pratt.[16] Jones, *et al.*,[17] found that the use of stainless steel wire in place of catgut in wound closure for abdominoperineal resections of the rectum had reduced the incidence of infections from 27.5 to 0.85 per cent. Disruptions after biliary surgery were reduced from 11 to 1.2 per cent. Kaufman, *et al.*,[18] in their study of alloy steel wire, observed that during the immediate postoperative course there was distinctly less induration, redness, and swelling of the tissues when wire was used than when other suture materials were employed.

In a description of disrupted wounds following closure with catgut, Fallis[19] noted "an inflammatory reaction characterized by excessive edema and outpouring of serum." Although an allergic phenomenon was suggested as an explanation, it is possible that this type of reaction could be caused by irritant hydrocarbons in the catgut.

The various reports which have been summarized bring out very clearly that there is an irritant factor in the use of catgut which is undesirable from the standpoint of optimum wound healing when comparisons are made with the various nonabsorbable suture materials. This irritant factor appears to manifest itself in the wound by induration, redness, serum formation, lowered tissue resistance, with increased susceptibility to infection from organisms introduced at operation or from the blood stream, and retardation of healing. The one point in common with the nonabsorbable suture materials which were used as a basis of comparison with the catgut, is that no extraneous irritant could be carried into the tissues with silk, cotton, or alloy wire because these are simply heat sterilized in the autoclave and then prepared for use at the operating table. Surgical gut, however, has customarily been provided in glass tubes, with either an anhydrous hydrocarbon liquid for boilable gut or an alcoholic solution for nonboilable gut. The anhydrous boilable tubing fluids have generally been xylene although in some instances may have been toluene. The alcoholic solutions of numerous products have been found to contain appreciable quantities of a hydrocarbon which is undoubtedly a residuum from the heat sterilization process which was not removed during the process of manufacture before the alcoholic solution was added and the tube sealed. Here, we have a common factor for the catgut, regardless of whether it was boilable or nonboilable, which is the irritant hydrocarbon in the tubing fluid which our studies have demonstrated. In view of our observations presented in this paper, it would appear that a fairly substantial part of the tissue irritation which these many observers have felt was characteristic of catgut when comparisons were made with the nonabsorbable

materials may be due to the irritant hydrocarbon carried into the tissues with the gut. The presence of alcohol in the gut from nonboilable tubing fluid or from dipping boilable gut in 70 per cent alcohol to induce pliability, undoubtedly, contributes in part to the tissue irritation. It is our opinion that the action of alcohol is of secondary importance but not necessarily negligible.

The various reports on the use of nonabsorbable material as compared with surgical gut must be further evaluated, of course, from the standpoint of size of suture material as well as the operative technic to arrive at a fair basis of comparison. Howes and Harvey,[20] in their extensive work on wound healing and suture material, have long stressed the importance of minimizing the bulk of suture material in wounds closed with catgut by resorting to the smaller sizes which they demonstrated to have adequate tensile strength in comparison with the strength of the tissues approximated. Their work has stimulated many surgeons to utilize a more meticulous technic, using relatively smaller sizes of catgut, which has resulted in a considerable improvement in clinical results with absorbable suture material. The minimizing of the bulk of suture material will, of course, decrease the amount of hydrocarbon introduced into the wound but would not eliminate this irritant factor. Dunphy and Botsford, in their comparative series of cases, where the catgut was used in relatively small sizes, by meticulous technic, found that there was still an appreciable difference between the silk and catgut series.

Kraissle,[21] in his review of suture material, brought up the point of chemical irritants in the catgut which may contribute to tissue irritation, such as the liberation of chromium; however, in a subsequent personal communication he was of the opinion that xylene tubing fluid may account for the tissue irritation observed with boilable catgut.

Furthermore, we believe that most of the excessive tissue reactions encountered in the previous work on the Absorption of Surgical Gut can be accounted for to a large extent by the irritant hydrocarbon factor of the tubing fluid. In reviewing the records of this work, it was found that the photomicrographs which portrayed the least evidence of polymorphonuclear leukocytic response of the tissues to the chromic catgut implants were from those products which were relatively free from irritant hydrocarbon in the tubing fluid according to tests carried out on tubes of catgut left over from these experiments. Also, it was found that those products which were characterized by excessive exudate and profuse polymorphonuclear leukocytic invasion of surrounding tissues, generally, had a high hydrocarbon content of the tubing fluid. Furthermore, some of the boilable products which were tested during this work but which were not reported in detail because the tissue reaction was so excessive that it was believed that some error in technic had occurred, undoubtedly derived their irritant properties from the xylene tubing fluid. In some of these tests the entire abdominal wall was edematous, and the sinus tract where the catgut implant was located had the appearance of having been seared by a cautery. Cultures of the exudate were usually

sterile. This chromic catgut usually disintegrated into shreds within a week or ten days.

In analyzing the action of the hydrocarbon in the tissues, it is probable that the excessive polymorphonuclear leukocytic response elicited by the irritant hydrocarbon contributes to a more rapid onset of the absorption mechanism. In the previous study, it was found that catgut was especially vulnerable to leukocytes. Wherever there was an excessive leukocytic response the catgut was generally rapidly absorbed, whereas catgut, which did not elicit an excessive leukocytic response, was generally absorbed over a long period of time by macrophages. On the basis of such observations, it was believed that there were two fundamental mechanisms of absorption—the leukocytic mechanism of rapid absorption; and the macrophage mechanism of slow absorption. The former was associated with extensive evidence of tissue irritation, the latter with minimal irritation.

It is probable, therefore, that the extraneous tubing fluid irritants induce a polymorphonuclear leukocytic response which hastens the onset of the mechanism of absorption. Once this leukocytic mechanism of absorption has started to break down the catgut it is not unlikely that the products of breakdown may further act as irritants to the tissues so that the irritation inaugurated by the tubing fluid may be enhanced or prolonged. The combination of these two factors may be important in the tissue irritation which has been observed with catgut. The elimination of the hydrocarbon irritant from the tubing fluid of chromic catgut is an important factor in obtaining relatively slow absorption by a predominantly macrophage mechanism, which is the characteristic tissue response to relatively inert foreign material. Even extensive chromicising will not protect the gut from the attack of an irritant induced leukocytic response, which then breaks down the catgut by the rapid absorption mechanism instead of by slow absorption. Therefore, chromic catgut which may be adequately chromicised by ordinary standards may undergo rapid loss of tensile strength and complete absorption before it has served its function of approximating tissues until strength from healing occurs if there is an extraneous irritant factor from the tubing fluid.

It was of considerable interest to find that the exudate which was formerly characteristic of many of the plain catgut implants was substantially minimized when these same products were subjected to thorough washing procedures. Plain catgut is more vulnerable to leukocytic absorption, and it is probable that a much smaller amount of irritant is required to induce the rapid absorption mechanism for plain catgut than obtains with chromic catgut.

SUMMARY

1. Weighing experiments have demonstrated that one to two per cent of the weight of boilable surgical gut was lost over a period of one to five days in a vacuum desiccator after elimination of the xylene tubing fluid on the surface of the gut. This weight loss probably represented the amount of xylene contained within the strand of gut. It is very doubtful that the usual

operating room procedures for inducing pliability of the boilable catgut, such as dipping in water or saline or 70 per cent alcohol would eliminate the xylene within the strand. Similar weighing experiments on nonboilable surgical gut have demonstrated that 18 per cent loss of weight occurred over a period of one to three days after removal of the catgut from alcoholic tubing fluid and subjecting the strand to stretching, as is customary in the operating room after removing the gut from the tube. In view of the observations previously reported by us, and Sidwell, that as much as five to ten per cent, or more, of the alcoholic tubing fluid may be composed of a high boiling range hydrocarbon it is assumed that the weight loss would account for a proportionate amount of this hydrocarbon. This would imply the presence of 0.9 to 1.8 per cent by weight of hydrocarbon in the catgut strand, which is comparable to the amount of xylene accounted for in the boilable gut.

2. Intradermal injection experiments in dogs and patients have demonstrated that 1 per cent, 0.5 per cent, and even 0.1 per cent emulsions of xylene or hi-flash solvent in saline will produce inflammatory lesions which are characterized by an initial capillary dilatation, edema, and subsequent leukocytic infiltration. These concentrations represented the injection of 0.43 mg., 0.215 mg., and 0.043 mg., respectively, of the hydrocarbons.

3. In correlating the weighing experiments with the injection tests, it would appear that the saline injections with one per cent hydrocarbon are comparable to the minimum concentration of hydrocarbon which was believed to exist in the gut under the conditions described. From the standpoint of actual amount of hydrocarbon, it should be pointed out that the intradermal injection of 0.043 mg. of xylene or hi-flash solvent was capable of producing an inflammatory lesion in the skin and that a single ligature of No. 1-size of catgut may contain more than twice this amount of hydrocarbon.

4. Implantation tests of surgical gut in the abdominal muscles of dogs demonstrate that the conspicuous tissue reactions which have been previously observed by us, and others, in the use of catgut may be substantially reduced if the catgut is thoroughly washed in 95 per cent ethyl alcohol and subsequently dried or washed in saline. This procedure did not always eliminate microscopic evidence of irritation, especially in such products as had a high hydrocarbon content of the tubing fluid. Elaborate washing procedures, however, are not recommended for preparation of catgut in the operating room.

CONCLUSIONS

1. The amount of irritant water-insoluble hydrocarbon from tubing fluids, which in ordinary operating room technic may be carried into the tissues along with surgical gut, is adequate to explain a substantial part of such tissue irritation as has generally been attributed to properties of the catgut *per se*. The presence of alcohol in the gut from nonboilable tubing fluid or from washing procedures for boilable gut probably contributes in part to such irritation.

2. From the standpoint of obtaining optimum wound healing in surgery,

it is obvious that the introduction of tubing fluid irritants into the tissues along with suture material is not in the best interests of the patient or the surgeon.

3. The elimination of tubing fluid irritants from surgical gut should result in generally better clinical results with the use of absorbable suture material.

Appreciation is expressed to Lillian Eichelberger, Ph.D., of the Dept. of Medicine for her cooperation in carrying out the weighing experiments.

REFERENCES

[1] Jenkins, H. P., and Hrdina, L. S.: Absorption of Surgical Gut (Catgut). I. The Decline in Tensile Strength in the Tissues. Arch. Surg., **44**, 881, 1942; II. Pepsin Digestion Tests for the Evaluation of Duration of Tensile Strength in the Tissues. Arch. Surg., **44**, 984, 1942; Jenkins, H. P., Hrdina, L. S., Owens, F. M., and Swisher, F. M.: III. Duration in the Tissues after Loss of Tensile Strength. Arch. Surg., **45**, 74, 1942; Jenkins, H. P.: IV. Recommendations for Absorbability and Digestibility Specifications. Arch. Surg., **45**, 323, 1942.

[2] Dunham, C. L., and Jenkins, H. P.: The Relation of the Tubing Fluid to the Tissue Reaction and Absorption of Surgical Gut (Catgut). Bull. of the American Coll. of Surg., **28**, 62, Feb., 1943; Jenkins, H. P., and Dunham, C. L.: The Irritant Properties of Surgical Gut Tubing Fluid. Proc. Inst. of Med. of Chi., **14**, 422, May, 1943.

[3] Dunham, C. L., and Jenkins, H. P.: Surgical Gut (Catgut) Tubing Fluid as a Tissue Irritant, ANNALS OF SURGERY.

[4] Sidwell, A. E.: Hydrocarbon Content of Nonboilable Surgical Gut Tubing Fluids. ANNALS OF SURGERY.

[5] Whipple, A. O.: The Use of Silk in the Repair of Clean Wounds. ANNALS OF SURGERY, **98**, 662, 1933; Choice and Use of Suture Material in Repair of Clean Wounds; *idem:* The Int. Abstr. Surg., **69**, 109, 1939; The Critical Latent or Lag Period in the Healing of Wounds. ANNALS OF SURGERY, **112**, 481, 1940.

[6] Meleney, F. L.: Infection in Clean Operative Wounds. Surg., Gynec. and Obst., **60**, 264, 1935.

[7] Guthrie, D., Brown, M. J., and Woodhouse, K. W.: The Advantages of Silk in General Surgery. N. Y. State Jour. of Med., **39**, 2011, 1939; *idem:* A Technique of Thyroidectomy Permitting the Use of Silk. Surg. Gynec. & Obst., **68**, 801, 1939.

[8] Puestow, C. B.: Comparison of the Use of Catgut and Silk in Thyroid Surgery. Surg. Clin. of No. Am., **20**, 241, 1940.

[9] Shambaugh, P.: Postoperative Wound Complications. Surg., Gynec. and Obst., **64**, 765, 1937.

[10] Shambaugh, P., and Dunphy, J. E.: Postoperative Wound Infections and the Use of Silk: An Experimental Study. Surgery, **1**, 379, 1937.

[11] Cutler, E. C., and Dunphy, J. E.: The Use of Silk in Infected Wounds. New Eng. Jour. of Med., **224**, 101, 1941.

[12] Dunphy, J. E., and Botsford, T. W.: The Use of Silk in Thyroid Surgery. Surg., Gynec. and Obst., **69**, 441, 1939.

[13] Meade, W. H., and Ochsner, A.: The Relative Value of Catgut, Silk, Linen, and Cotton as Suture Materials. Surgery, **7**, 485, 1940; *idem:* Spool Cotton as Suture Material. Jour. Am. Med. Assn., **113**, 2230, 1939; Meade, W. H., and Long, C. H.: Cotton as a Suture Material. Jour. Am. Med. Assn., **117**, 2140, 1941.

[14] Babcock, W. W.: Wounds and Their Complications. Am. J. Surg., **36**, 3, 1937; Catgut Allergy with a Note on Use of Alloy Steel Wire. Am. J. Surg., **27**, 67, 1935; *idem:* Ligatures and Sutures of Alloy Steel Wire. Jour. Am. Med. Assn., **102**, 1756, 1934.

[15] Preston, D. J.: The Effect of Sutures on the Strength of Healing Wounds. Am. J. Surg., **49**, 56, 1940; *idem:* The Mechanical Superiority of Annealed Stainless Steel Wire Sutures and Ligatures. Surgery, **9**, 896, 1941.

[16] Pratt, G. H.: Nine Years Clinical Experience with Steel Wire as Suture Material. Surg., Gynec. and Obst., **74**, 845, 1942.

[17] Jones, T. E., Newell, E., and Burbaker, R. E.: The Use of Alloy Steel Wire in Closure of Abdominal Wounds. Surg., Gynec. and Obst., **72**, 1056, 1941.

[18] Kaufman, L. R., Johnson, W., and Lesser, A.: A Clinical Study of Alloy Steel Wire Sutures. Surg., Gynec. and Obst., **69**, 684, 1939.

[19] Fallis, L. S.: Postoperative Wound Separation: Review of Cases. Surgery, **1**, 523, 1937.

[20] Howes, E. L., and Harvey, S. C.: The Strength of the Healing Wound in Relation to the Holding Strength of the Catgut Suture. New England M. J., **200**, 1285, 1929; *idem:* Tissue Response to Catgut Absorption, Silk, and Wound Healing. Internat. J. Med. and Surg., **43**, 225, 1930; *idem:* Clinical Significance of Experimental Studies in Wound Healing. ANNALS OF SURGERY, **102**, 941, 1935; Howes, E. L.: The Immediate Strength of the Sutured Wound. Surg., **7**, 24, 1940; *idem:* A Renaissance of Suture Technique Needed. Am. J. Surg., **48**, 548, 1940.

[21] Kraissl, C. J.: Suture Material: A Review of Recent Literature. Internat. Abstr. Surg., **62**, 417, 1936; and personal communication.

SURGICAL PRINCIPLES OPPOSED TO "RULE-OF-THUMB" IN THE TREATMENT OF COMPOUND FRACTURES*

CLAY RAY MURRAY, M.D.
NEW YORK, N. Y.

THE TREATMENT OF WOUNDS embraces a large part of the horizon of surgical interests at the present time. This, naturally, has been productive of marked increase in the number and range of investigative activities on the subject of compound fracture treatment. In studying the prolific literature in this field covering the last year or two, one is struck by the predominance of statistical analyses based on the effect of single factors in treatment. From the statistical side, some of the work has been very accurately, conscientiously and painstakingly done, with conclusions based on what mathematicians term "statistically significant figures." The punch-card system of analysis has been a great aid in the gathering of such actuarial figures. These may accurately indicate the percentage chance which a wound has of escaping infection under the routine use in a consecutive series of cases of a given procedure or a given combination of procedures. On the other hand, such data are of very doubtful value as criteria for the treatment of any given patient. Moreover, I feel moved to question seriously the wisdom of attempts to establish procedures for routine application in the treatment of compound fractures. No matter how sound the statistical basis for the conclusions drawn as to the percentage of success which may be expected from the routine employment of a given therapeutic procedure *in a large series of cases*, the adoption of that procedure as a routine automatically dooms to failure, from the outset, a certain percentage of them. To make such data of clinical value in the treatment of the *individual case*, it is of vital importance that we know when *not* to follow a procedure which is ordinarily successful. In other words, it is essential that we employ no procedure which has a percentage of failures as a routine, but that we establish criteria enabling us to judge as to when its use is sound or unsound, in order to eliminate, insofar as possible, the failures inherent in the use of a routine procedure. This cannot, unfortunately, be based upon the study of individual factors. Every compound fracture presents a closely knit combination of a large number of factors which must be considered, so to speak, as a word, not as a group of letters. A given group of letters can give a great many different answers in the way of words dependent upon the arrangement and relationship of the letters. Our interest must be in what the letters spell as much as in what they are. The possible combinations of the large number of factors encountered in the treatment of compound fractures are numerous and widely varied. If all the permutations of such combinations could be accurately plotted, with an indicated course of procedure for each permutation, there would be no need for such things as surgical judgment or surgical principles.

* Read before the American Surgical Association, May 13–14, 1943, Cincinnati, Ohio.

We could then have *rules* for treatment. I have no doubt that this might be a mathematical problem capable of solution; but it would entail a statistical study somewhat astronomic in proportions and bewildering in its complexity.

I have no doubt that at least some of the studies being made on the effects of individual factors in treatment are planned as preliminaries to studies of the effects of various combinations of factors and on the interrelationships of those factors. This tends to lead to the weltering complexity of statistical study suggested above. Unfortunately, and I am certain, contrary to the desires of some of those making such preliminary studies, the statistical data to date are being too generally interpreted in terms of rules for action. When a statistical study of the results of wound closure in compound fractures is announced showing that, in a given series, a higher morbidity to infection was observed in those left open than in those closed, the popular interpretation is apt to be in terms of the dictum "close your compound wounds." The statistical results in a series may continue to be favorable following such a rule, but the results to certain individuals in the series are disastrous, although it may well be that the author had neither the intention nor desire to have his statistics so interpreted. Similar rather general false interpretations, for instance, have resulted from statistically accurate findings that extensively "débrided" wounds show a higher morbidity to infection than do those minimally "débrided," and that wounds in which extensive or prolonged lavage has been used show a higher rate of infection than do those in which little or no lavage has been used. Another way of interpreting such findings might be, perhaps, that wounds of such character and extent as to call for extensive débridement and lavage are apt to show a higher morbidity to infection than those not requiring such treatment. This, of course, is quite a different viewpoint.

Have we any criteria, apart from statistical studies, on which to base the procedures to be used *in the individual* case, and are those criteria a sounder basis for the treatment of the individual than such statistical data as we have indicated above? I believe the answer to both questions is in the affirmative, and that the criteria are what are known as surgical principles, and that the rôle of statistical study should be principally to analyze the failures of any given procedure from the standpoint of what surgical principles were violated in the use of the procedure in those cases. If our accepted surgical principles are wrong, we should abandon them, and should evolve and adopt other criteria which permit us to decide as to what is the best thing to do for the problem presented by the individual patient, rather than criteria which determine what procedure can be used in a large series of cases with the least number of preordained individual failures.

I believe that a logical analysis of the whole problem allows us to establish relatively simple criteria on the basis of which we can decide in the individual case what procedures should be used, and how they should be used. Such an analysis is no more than a review of established surgical principles and standards and their bases. Of this I am well aware, but it appears to me

not only timely, but a sober and steadying influence which may not be amiss. It should embrace discussion of:

1. The problem presented by a compound fracture.
2. The necessity for regarding the wound and the fracture as parts of of the same problem.
3. The necessity for dealing with both these problems simultaneously at all times.
4. What it is desired to accomplish for the wound and for the fracture by the procedures employed.
5. The basis for decision as to procedures to be employed in any individual case.
6. The procedure now in common use or advised for common use from the standpoint of the accomplishment of treatment aims.

1—THE PROBLEM PRESENTED BY A COMPOUND FRACTURE

This may be very simply stated in broad terms. The problem is that of preventing the *translation* of contamination into clinical infection if possible; the minimizing of the damage done by infection if it develops; the healing of the damaged tissues in as short a time as possible with a minimum of residual tissue disability and deformity. All the indications for therapy to bone and soft parts are contained in this statement.

2—THE NECESSITY FOR REGARDING THE WOUND AND THE FRACTURE AS PARTS OF THE SAME PROBLEM

This is a vital viewpoint in the formulating of sound principles for treatment in compound fractures. There is often a distinct tendency to regard the wound of the soft parts and the wound of the bone as different problems requiring separate consideration. Nothing could be more deterrent to sound and logical consideration of treatment. The soft part lesion cannot be treated as one entity in accordance with certain principles and standards, and the bone lesion as another and separate entity involving the employment of different principles and standards. This is true whether considering the problem from the standpoint of infection, of wound healing, or of residual disability or deformity.

3—THE NECESSITY FOR DEALING WITH BOTH THESE PROBLEMS SIMULTANEOUSLY AT ALL TIMES

It is essential at all times to regard what is being done as being done for the whole wound and to view each procedure used from the standpoint of its effect in meeting the general problem in both bone and soft parts. The viewpoint that our first or major consideration should be the question of infection in the soft parts may lead to deplorable results in the bone lesion. The viewpoint that the accurate reduction of the fracture is the essential feature of treatment may lead to regrettable soft part complications. The realization that the treatment of both bone and soft parts is based on the simultaneous application of the same principles to both lesions at all times

leads to a minimum of residual damage in both. This essential viewpoint is brought out in the discussion of procedures which follows.

4—WHAT IT IS DESIRED TO ACCOMPLISH FOR THE WOUND AND FOR THE FRACTURE BY THE PROCEDURES EMPLOYED

This is, in effect, the answer to the question: "How do we attempt to meet the problem stated under 1, above?" We may express our desires and the reasons for them as follows.

If the Lesion is in the Stage of Contamination:

a. For obvious reasons, to remove as much of the contamination as possible, *and to add* as little as possible. We must realize that we cannot remove all contaminating organisms, and that the tissues have to deal with those left behind.

b. To remove as much dead and obviously devitalized tissue as possible with as little additional damage as possible. Dead and devitalized tissue acts as a culture medium to furnish pabulum for the organisms left behind. Through the local accumulation of products of its autolysis it is a definite handicap to the biochemical progress of bony healing in fracture. Primary fracture healing must be conceived of as taking place in the tissue immediately surrounding the fracture rather than from bone-end to bone-end, and optimum conditions for primary fracture healing demand the presence of living vascular tissue for the production of the undifferentiated connective tissue about the fracture site which is the medium for so-called primary callus formation. From the standpoint, then, of both wound and fracture healing, as well as from the standpoint of minimizing the chances of *translation* of contamination into infection, the elimination of dead and devitalized tissue insofar as is possible is a sound desideratum.

c. The elimination insofar as possible of dead spaces within the wound. This is a principle accepted as sound in all other surgical procedure. It should be sound here. It involves not only the surgical exposure and elimination of dead spaces where indicated but also particularly meticulous hemostasis—the approach to a dry wound—to obviate the creation of dead space containing pabulum for bacteria by the formation of subsequent hematomata. As adequate a reduction of the fracture as is possible is an obvious corollary of this principle, if it be sound.

d. As adequate and accurate a closure of the wound as is possible without the creation of tension within it at the time of closure *or subsequent to the time of closure*. The closure we desire to shorten the healing time, to minimize the subsequent scarring and deformity, and to minimize the opportunity for subsequent additional contamination of the wound. The principle applies to the closure of the bone portion of the wound—*i.e.*, fracture reduction—as positively as it does to the soft part of the wound. We desire to avoid tissue tension because we believe that its existence leads to impaired wound healing, and to impairment of the tissues' ability to deal with the organisms still remaining in them. In addition, tension in the soft parts surrounding the bone seriously impairs the minute circulation therein—

the circulation of the fluids in the tissue spaces, the lymphatics, and the ultimate capillaries. It is this circulation which is of such vital importance in restoring, after injury, the biochemical status in the tissue fluids which is essential to the deposition of calcium in the healing tissue about bone to form callus. From the dual standpoint, then, of preventing the *translation* of contamination into infection and of promoting bone and soft-part healing, the development of tension within the tissues of the wound must be prevented at all times. From this standpoint, the accuracy of reduction of the fracture itself—*i.e.*, the closing of the bone wound—must be considered from the standpoint of the degree of violence necessary to attain complete and accurate reduction in terms of resultant tissue damage, inflammatory reaction, and resultant tension within the tissues. Complete fracture reduction, simultaneously with complete wound closure, is ideal and desirable. The real question to be answered in the individual case is to what degree is it wise and safe.

e. Rest of the wound until the risk of *translation* of contamination into infection has been passed, and until the healing of the wound has been adequately initiated. This applies, if the principle be sound, equally to both soft parts and bone as part of the same problem, although chronologically the answers to the two are different. Rest of the noninfected wound in the soft parts until healing is adequately initiated is a question of days. Rest of the noninfected wound in the bone, on the same basis, is a question of weeks. The necessity for contaminated bone and soft-part wound rest, until the period of infection risk is passed and until healing in each is adequately initiated, is absolute. The ideal treatment would allow of functional activity of the soft parts and bone, if possible, simultaneously at the early date. It is possible by some methods of treatment for the bone wound to accomplish an approach to this ideal. To be safe and successful they must maintain rigid fixation of the bone fragments—*i.e.*, bone wound rest—until the healing of the bone wound is safely established—*i.e.*, until callus formation is adequate to maintain the edges of the bone wound from separating—while functional activity of the extremity is being carried out. Rigidity of fixation of the bone fragments in compound fractures, because of this factor, is even more important than in the simple fracture. I am certain that mobility at the fracture site is a potent factor in determining whether or not contamination in compound wounds is *translated* into infection and whether or not the bone is involved seriously if infection does develop.

If the Lesion is in the Stage of Infection:

Treatment of these wounds is on an entirely different basis from that governing the treatment of contaminated wounds. The surgical principles underlying the treatment of infection are to provide adequate drainage with the elimination of pocketing; to remove any foreign material present; to avoid opening up channels for spread of infection; to provide rest for the wound until the infection is adequately controlled; and to provide the patient with whatever aid we can to enable his tissues to control it. These principles again apply equally to soft-part wound and to bone wound, and, obviously

and grossly, modify our procedure. No question here of débridement as hereinafter defined, no question of closure.

5—THE BASIS FOR DECISION AS TO PROCEDURES TO BE EMPLOYED IN ANY INDIVIDUAL CASE

a. Is the case contaminated or infected? In some respects this is a good deal like asking the question: "How long is a piece of string?." However, there are certain definite things one can say. In the first place, all compound fractures are either one or the other, whether the compounding has occurred from within or from without. If they are considered contaminated they should be treated as contaminated cases. If they are considered infected they should be treated as infected cases. Too often, the procedure adopted attempts to split the difference, or the wound is considered neither infected nor contaminated—a dangerous attitude to assume. The extent of the procedure followed must be influenced by a number of factors. The number of hours elapsed between time of injury and time of wound treatment is by itself an inadequate criterion as to the probable status of the wound. The circumstances under which the wound was received (to include the locale, possible types of contamination, the probable habitual condition of cleanliness of the patient's skin and clothing covering the wounded region); the type and severity of the violence and the amount of tissue damage present beneath the skin and subcutaneous tissue rather than the size of the skin wound; the adequacy and promptness of the first aid treatment accorded both soft-part and bone wounds; all these must be considered in addition to the actual lapse of time in deciding the question in terms of wound pathology.

Each of the possible combinations of these various factors has a different significance in determining whether or not the lesion should be viewed as contaminated or as infected, and, therefore, as to what principles should be followed in handling it.

The amount of tissue removal to be practiced in a given contaminated case must be determined by not only the amount of tissue damage present, but by the nature of the damaged tissue and the potential disabilities or risks occasioned by its removal, the amount of gross contamination present, the press of time by reason of the patient's condition, or by reason of other factors at times encountered—particularly in military surgery—and by the region of the body involved. Upper and lower extremity wounds differ remarkably and radically in respect to healing characteristics and morbidity to infection, although all other factors involved may be apparently identical.

The extent to which the wound may have to be extended will be governed by the size and location of dead spaces, by the evidence of tissue damage and contamination, by the necessities of adequate hemostasis, and by the difficulties to be encountered in wound closure.

The necessity for cleansing, but nonirritating lavage of the wound, and the amount of such lavage, will be governed by the size of the wound, by the amount of gross contamination originally present, and that, of necessity,

left behind after tissue removal, by the presence or absence of foreign bodies within the tissues, by the number of clots encountered and by evidence of contamination having been carried into the depths of the wound.

The degree of accuracy of reduction of the fracture, and the method employed in attaining it, must be governed by the nature and location of the bone injury, by the time available for the procedure, by the amount and significance of the additional trauma inflicted and by the equipment and assistance available for carrying it out. The method to be employed in the individual case is that method which, under all the particular circumstances, will come nearest to an ideal of "wishing" the fragments into satisfactory position. And no matter what method is used, it must be employed with this object in mind and not merely with the object of restoring bony anatomy as evidenced roentgenologically. This is the closure of the bone wound, and it should be governed by precisely the same principles as closure of the soft-part wound.

The closure of the soft-part wound must be governed by evidence of the creation of tension at the time of closure, the creation of tension later by reason of inflammatory swelling in the tissues, the degree of hemostasis obtainable at the time of closure and immediately thereafter by pressure dressings, *etc.*, the degree and type of contamination present originally and after wound toilet, the amount of dead and devitalized tissue left in the wound, the presence or absence of foreign bodies and the necessity or advisability for coverage of structures which, uncovered, do badly (such as tendons, nerves, periosteum stripped of soft parts, and the actual site of fracture). Exposed periosteum, stripped of soft-part attachment or coverage, acts much like exposed tendon.

The degree and extent of time to which rest of the soft-part portion of the wound must be employed is dependent upon local circulatory factors, on the degree of healing necessary to permit functional activity of the particular soft parts involved and on the tension to which that soft-part healing is subject by reason of difficulties of closure, rather than by the length of the wound, in addition to the time necessary to be reasonably certain that the contamination left in the wound has not been *translated* into infection. The fact that wounds heal from side-to-side and not from end-to-end, is of importance in this respect. The degree and extent to which rest of the bone portion of the wound must be enforced by immobilization of the whole portion of the body involved is dependent upon the availability of equipment and skill for the carrying out of the various methods employed. In general, that method is most advantageous which allows of the greatest degree of voluntary muscular activity without endangering the rigidity of fixation of the bone fragments at the fracture site. The healing of the fracture site is the bone wound healing, and the wound edges must be kept at rest until the healing is sufficiently established to stand the strain of functional activity. On the other hand, there is no question but that voluntary activity of the *muscles* of the part is a potent factor in determining the probability and

speed of progress of bone healing, provided the bone fragments are at rest. In the employment of any method, then, one must aim at securing the maximum of voluntary muscular activity consistent with rigidity of the fragments at the fracture site—no more and no less.

6—THE PROCEDURES NOW IN COMMON USE OR ADVISED FOR COMMON USE FROM THE STANDPOINT OF THE ACCOMPLISHMENT OF TREATMENT AIMS

Emergency or First Aid Treatment:

To properly aid in the carrying out of sound principles of treatment this should be applied as soon after injury as possible without adding to, or more widely distributing, the wound contamination already present and should protect the wound from further contamination and should control hemorrhage. It should render and keep the injured soft parts and bone as quiet as possible until definitive treatment is undertaken, and should inflict as little additional trauma as is possible. Abstinence from washing about the wound or the use of antiseptics as first aid measures is indicated. The prompt covering of the wound with adequately protective sterile dressings, of the pressure dressing type if necessary to control hemorrhage, is indicated. Tourniquets are contraindicated unless pressure dressings fail to control bleeding. As extensive immobilization as possible, preferably with the employment of constant fixed traction, is indicated. As regards the prophylactic use of chemotherapy, locally and by mouth, there would seem to be certainly no contraindication provided that if used locally in the wound it is as a thin film rather than in large masses and provided that by either mode of administration it is not relied upon to make it safe to delay definitive wound treatment. By the at present available data, chemotherapy must be used as a hope in the event of unavoidable delay, and as a hope in the attempt to prevent local or general sepsis. It must, as yet, be regarded as an adjuvant to surgery, and not as a substitute for it. I do not believe its use warrants the abandonment, in any respect, of what have, up to now, been considered sound surgical principles or of the procedures properly employed to carry out those principles.

The Employment and Character of Wound Débridement or Wound Drainage:

I must preface my discussion of this point with an apology to purists for my use of the term "débridement" in describing what I have in mind. I am aware that the term in its strict and literal sense does not embrace all that I use it to describe. By débridement I mean the removal of dead, devitalized and contaminated tissue from a contaminated wound, with the elimination of dead spaces and foreign bodies within the wound. To be justified, débridement must be undertaken for a contaminated wound, and it must remove as much of the affected tissue as possible and eliminate dead spaces and foreign bodies, in keeping with the principles previously stated. A so-called débridement which does not accomplish this, or one which distributes contamination more widely which removes clean and viable tissue which inflicts an appreciable amount of damage in the doing or which

creates dead spaces within the wound, is insult added to injury. It is not good surgery. In an infected wound, as gauged by the probabilities evaluated heretofore, drainage should be adequate for the infected area, preferably dependent, should attempt no removal of tissue other than surface contamination, and should remove foreign bodies, when possible. Invasion of sound tissue violates principles.

Lavage of the wound should have for its purpose removal of contamination from the wound. To accomplish this it must proceed from the base of the well-retracted wound, with sufficient head to give a visible and forceful flow from the depths outward. The amount of saline used (and saline is adequate) is far less important than the rate and force of flow. A lavage so conducted that the fluid lakes in the wound, with little if any force of flow, serves probably to generally distribute what contamination is present. It is obviously not carrying out the principle involved. One might make the comparison between the cleansing effects of a tub bath and of a shower. In a tub bath the individual laves all parts of his body in the contamination from all other parts; in a shower he washes the contamination from his body. Lavage of a wound should have the effect of a shower from within, not of a tub bath.

Local chemotherapy following this wound toilet must be subject to the same restrictions as mentioned in discussing its prophylactic employment. I do not believe there is, at present, justification for altering the surgical criteria for wound closure in any respect because of the use of chemotherapy on the basis of the data now available. Systemic chemotherapy is justified, but only on the same basis, with the added warning that severe kidney and liver damage can result not only from overdosage, but from extremely moderate and short-lived dosage in susceptible individuals.

Wound Closure—Soft Part:

No one can deny the advantages of a closed wound over an open one from the standpoint of wound healing time and character, the minimizing of secondary contamination, and from the standpoint of aid in the bone healing process. Tension, at the time of closure, or later, is a definite threat, however, which may far outweigh these advantages. The degree of tension to be risked must be based upon an evaluation of the various factors listed under the principles involved in wound closure as present in the individual case. The use of releasing incisions, of flaps, and other plastics must be considered, and may be of advantage in securing closure without tension. The use of elevation and of pressure dressings may be of distinct aid in preventing intratissue tension during the inflammatory reaction in the subsequent days. When, however, primary closure entails a degree of tension which, in the individual case, is a definitely recognized, or even probable, risk, I feel strongly that it requires considerable justification. The placing of untied sutures with a view to a delayed closure guided by the same principles when, and if, the wound has proven clean, or no closure at all is, I believe, a safer and sounder practice, more in keeping with surgical principles.

Wound Closure—Bone:

The bone wound should be closed—that is, the fracture should be reduced—at the time of soft-part wound closure. It should be accomplished to the maximum degree possible without violating the principles laid down previously, and by the method which under the circumstances of equipment and personal skill is apt to inflict the least damage commensurate with reduction adequate for the part involved. It is unsound thinking to label one method as universally preferable to another. Familiarity with all the potentialities of a theoretically inferior method combined with the skill and armamentarium adequate to *translate* those potentialities into fact are far more important factors than the theoretic excellence of a method in the absence of similar familiarity, skill, and adequate armamentarium, in deciding the method to be employed in carrying out fracture reduction that is sound in principle. The essential thing is that no matter what the method used, it must be used to its maximum efficiency in putting those principles into practice.

The same commentary holds true as to the methods to be considered for giving rest to the bone wound—fracture fixation or immobilization. No matter what the method used, it should be employed so as to exert, to the maximum, its potentialities in giving rigid fixation or rest to the fracture site, or bone wound, until the bone healing process is capable of functional strain, and it should employ, to the maximum degree possible, voluntary muscular activity as soon as fear of *translation* of contamination into infection has passed and the soft-part wound healing is capable of standing the strain of functional activity.

Time does not permit of the detailed evaluation of the various methods of fracture reduction and fixation from the standpoint of their mutual theoretic advantages and disadvantages. That they, one and all, should be used to carry out, to the greatest degree possible, definite principles, is the essential feature for the successful use of any of them.

DISCUSSION.—DR. FRANK L. MELENEY (New York): Doctor Murray has obviously directed his criticism at the statistical study of contaminated wounds, the results of which have been reported (ANNALS OF SURGERY, **118**, 305, August, 1943). If one goes about *trying to prove* something by means of statistics, I admit that figures can be distorted so as to simulate proof but if one goes about *trying to find out* something, statistics may be of real value. This we have tried to do.

Statistics so studied are more likely to bring out and support principles than they are to lay down "rules-of-thumb." "Rules-of-thumb" are characterized by having no weights or measures. They are what a cook uses to bake a cake, and a good cook can make a good cake, and a bad cook, a very bad cake by "rules-of-thumb." But that is precisely what statistics are not. Summary sheets which attempt to cover all of the factors involved in a given problem permit more or less precise measurement of these factors, and punch-cards which permit cross tabulations permit an evaluation of the relative importance of the various factors involved. Figures so obtained must then be subjected to the formulae of the biostatisticians in order to rule out the element of chance.

Under these circumstances, if statistically significant figures are obtained which seem to conflict with a principle, we must study the matter carefully to find out if it was really a principle or a preconceived notion.

Doctor Murray has been a student of fractures for many years and has worked out certain principles for their treatment which I will not question. But during the past year, while he has been directing one of our units studying compound fractures, he has seen more compound fractures than in all of the ten years preceding. And I know, for a fact, that he has modified some of his methods of treatment, and I believe he has modified some of his ideas about them, perhaps not as a result of our figures as much as the result of his own experience. If he had not learned something during the past year I would have questioned the elasticity of his cerebral arteries.

It is a duplex if not a complex problem. It combines the problem of the healing of the bone and the problem of healing of damaged soft parts in the presence of bacterial contamination, the nature and extent of which the surgeon does not know when the case comes to his hand. The sooner he does know that, the better will he be able to evaluate the possibility of his attaining his purpose of getting bony union and soft part function and of preventing infection. The underlying principles directing the surgeon to accomplish the desired end-result with regard to healing of the bone and the free movement of surrounding muscles and neighboring joints may be in conflict with the principles underlying the prevention or treatment of infection. Frequently it is necessary to compromise one principle to gain the other. For example, to get good alignment and approximation of bone ends it is important to preserve as much of the bone as possible. However, badly contaminated bone ends or detached fragments may be retained when, from the point of view of infection, the contaminated bone and loose fragments should be removed. Similarly, the insertion of a foreign body, like a metal plate and firmly driven screws, may immobilize the bone fragments but carry organisms deeply into the bone and cause necrosis of bone around screw-holes or next to the plate. There is always some bone necrosis around skeletal traction wires or pins or skeletal fixation pins, and necrotic tissue is a fertile soil in which infecting organisms may gain a foothold. The desire to obtain early function of surrounding muscles and joints may urge early motion when, from an infection standpoint, immobilization of both joints and muscles would seem to be indicated.

Recently, another factor has come in which must be considered and evaluated, namely, chemotherapy. That may involve a conflict of principles. The new drugs may inhibit bacterial activity and, at the same time, interfere with wound healings, act as foreign bodies, or change the metabolism of the tissues so as to materially delay bony union.

It is only by studying the cases as a whole as well as individual cases, trying to measure and weigh as accurately as possible the result and the effect of these new agents of treatment, that we can gain knowledge which will further improve our results in this interesting and complicated field of surgery.

Dr. Calvin M. Smyth, Jr. (Wynnewood, Pa.): It is a relief to hear somebody reemphasize the fact that general surgical principles have not been thrown out of the window by the introduction of chemotherapeutic measures.

Two years ago, before this Association, I had the privilege of discussing Dr. Philip Wilson's paper on compound fractures, and, at that time, I had occasion to say that we had been using the closed plaster encasement treatment of compound fractures for some fifteen years and that, while during the past two years we had introduced sulfa drugs into the wound in the treatment of compound fractures, we had failed to see any difference in the results that we obtained since the introduction of sulfa drugs over the results we obtained previously.

I am glad to say that we have the courage of our convictions, and for the past year have introduced no sulfa drugs into the wounds of compound fractures that were brought to definitive surgery within the time limits ordinarily accepted for débridement.

I want to thank Doctor Murray for bringing this matter before the Association, and I think that a few contributions of this sort will serve to prevent the treatment of compound fractures and wounds from being turned back seventy-five years. Certainly there were heroes before Agamemnon, and heels before Achilles.

Dr. Fraser B. Gurd (Montreal, Canada): I want to support what Dr. Calvin Smyth has said in reference to the value of Doctor Murray's contribution. I am not quite sure that seventy-five years regression might take place, but the unquestionable surgical principles must hold if we are to treat wounds in this war and in industrial and road accidents, and during and following the war.

At the risk of perhaps appearing to be facetious, I shall read over ten principles, as I see them, that make for adequate wound healing, whether such wounds be associated with fractures or not. They are all, as you will notice, based upon the letter "E." If any one of these features is not possible, difficulties are certain to rise later in the course of the individual case:

(1) Early operation; (2) enlargement of the wound in order that interstitial tension may be overcome and prevented; that (3) exploration of the wound may be adequately carried out; that (4) extraction of foreign bodies may be brought about; (5) excision of devitalized tissue may take place; (6) the exhibition of germicides and bacteriostatics; (7) the establishment of (curtain) drainage; (8) encapsulation of the part for the exclusion of secondary infection; (9) efficient immobilization, whether that be by plaster or by other means; and (10) the elimination of frequent dressings.

Dr. William Darrach (New York, N. Y.). I do not want to discuss principles and I do not want to discuss statistical methods. I do not want to discuss chemotherapy. I would like to bring out what our main objectives are in treating compound fractures.

First and foremost, comes the saving of life. Second comes the eventual return of function to the highest possible degree. Third comes the cutting down of the period of disability.

If we try to lay down flat rules, which will be followed under all circumstances, we are lost and beaten at the start. I think today, with the problem brought to such great importance because of war conditions, the question of surgical judgment is brought into play much more than it is in civilian work.

In civilian work, Albert Key, and a few other lucky men, can close all their compound fractures. Under battle conditions I think very few can.

In applying surgical principles we have to use horse-sense and surgical experience to the nth degree. The multiple factors that enter into a decision, which must be made without bacteriologic evidence, because that is lacking at the time of the primary operation, require everything that we can put into it.

Some of these factors are: The condition of the patient at the time he was injured; the condition of his skin and the parts of his clothing; of the terrain; of the injuries associated with that compound fracture; with the time elapsed since his injury; the kind of the first-aid treatment he had, from the time he was hurt until he came into the operating room; the amount of immobilization he had during that time; and the amount of time that can be spent by the surgeon on that individual case, which will depend on whether the case comes to him in a quiet lull, when he can spend all the time he wants, or whether he is rushing through a large batch of wounded.

Those are simply a few of the factors which must enter into the primary decision as to just what you are going to do at the time with that individual case. How are you going to save his life? How are you going to give him a serviceable leg or arm? How long is he going to be disabled?

I think unless we have something to fall back on, besides a flat "rule-of-thumb," whereby we have to "use our beans," we are not going to give these boys a square deal. For that reason, I think that if we can learn and understand, and then apply, with surgical judgment, fundamental principles, we will get farther than if we try to treat them all by some flat rule.

Dr. Clay Ray Murray (New York, N. Y., closing): There is little to say in closing this discussion except to reply to some of the comments made.

It is perfectly true, as Doctor Meleney has stated, that we have introduced some changes in procedure into our treatment of compound fractures at the Presbyterian Hospital since this study began. These changes were introduced in order to aid the

study and not because of change in our attitude. As a result of a year's experience with those changes I am firmly convinced that the major ones were ill-founded and should be discontinued.

As regards the use of chemotherapy it can be safely said that there has been, to date, no convincing evidence to prove that the introduction of chemotherapy into a compounding wound has exerted any influence on the morbidity of such wounds to infection. The original report of the cases at Pearl Harbor made strong claims in this regard, but subsequent developments in the same cases have cast a great deal of doubt on the validity of the original reports.

On the other hand, there is no convincing proof that chemotherapy intelligently employed locally has done any harm to the patient. It has been claimed that local chemotherapy interferes with wound healing, but it is considered probable that ill effects on wound healing have, at least in many instances, been due to the use excessive amounts rather than to the action of the drug itself. Basing our opinion on the consensus rather than on the opinion of any one investigator we must conclude that there has been no conclusive evidence adduced to support the idea that local chemotherapy is harmful. I can, therefore, see no objection to its use—in fact, I think it should be used. I think, however, that it should be used as a hope and not as a reliance, and most certainly not as a substitute for the adequate carrying out of sound surgical principles.

Débridement, as the term is commonly understood, and lavage have been brought into serious criticism by some investigations. Débridement is designed to remove dead and devitalized tissue, to remove contamination, and to eliminate dead spaces in the wound. If done so as to carry out these purposes the procedure is sound. If, on the other hand, it is so carried out that infection is carried into the depths of the wound and extensive tissue damage is inflicted, it should not be done. Lavage of the wound has been criticized because statistical evidence seems to show that those wounds which are extensively lavaged have a higher rate of infection than those less extensively lavaged.

This can be stated in quite a different way, as I have noted in the paper. There is, however, this additional point to be considered in lavage: The procedure is supposed to remove contamination, not to introduce it. In considering this factor, one might stress the comparison between a bath and a shower. When an individual takes a tub bath he merely assures himself of the fact that he has evenly distributed all over his body the contamination present on any one part of his body. When he takes a shower, on the other hand, he washes from his body all contamination. If a wound lavage is done using a low head of pressure for the solution, so that the fluid stays laked in the wound for the most part, and if the tube introducing the fluid is placed in the superficial parts of the wound, the procedure may introduce and distribute infection —it is a wound tub bath. If the lavage is done with a soft rubber catheter carefully introduced to the depths of the wound and with a head of pressure sufficient to produce visible forceful and outward flow of the fluid, it removes contamination from the wound—it is a wound shower from within.

I should like to say that the thoughts expressed by Doctor Darrach have been considered in the paper as prepared for publication, not only in regard to the principles involved but in reference to the rationale by which methods of treatment carry out these principles. The emphasis should be placed on the principles to be carried out rather than on the method by which they are carried out. The tendency is to place stress on the routine use of a method. A method of procedure which will produce satisfactory results in 90 per cent of the cases on which it is routinely used excites in me the most heartfelt sympathy for the unfortunate ten per cent who are doomed to failure from the beginning by the routine use of the method, and who are statistically insignificant.

THE MEDICAL TREATMENT OF HEMATOGENOUS OSTEOMYELITIS*

D. E. Robertson, M.D.

Toronto, Canada

This acute disease of childhood and adolescence and, infrequently, of adult life, is mainly due to staphylococcus or streptococcus. Of the two organisms, staphylococcus caused over 90 per cent of all cases in this and other series.[1] The organism gains entrance to the blood stream through lesions of the skin, of the mucous membrane, or the tonsils. The blood becomes contaminated and the organisms are deposited in certain areas of the body. It has been shown experimentally that viscera, muscles and bones may develop abscesses. In bone the areas involved are the epiphysis, the metaphysis, and the periosteum. There has been much work done to explain the occurrence of abscesses at these situations.[2, 3]

A study of the autopsy records of patients dying of this disease shows the same distribution of abscesses as in the experimental animals dying of it (Table I). The picture presented is that of a general infection. Heart,

Table I

Results of autopsy in 51 cases of acute osteomyelitis

Total number of autopsies	51
Acute pericarditis	33
Acute pleurisy or empyema	10
Abscesses or infarctions in lungs	22
Abscesses in kidneys	16
Acute arthritis	9
Metastatic osteomyelitis	4
Subcutaneous and intermuscular abscesses	9
Abscesses in myocardium	7
Abscesses in thyroid gland	1
Abscesses in spleen	3
Abscesses in prostate	1
Abscesses in liver	2
Acute duodenal ulcer	1
No pyemic lesion found	6

kidneys, liver and spleen are involved with inflammatory areas. The lung has areas of patchy pneumonia, and thrombophlebitis is prominent in all lesions. In view of these findings it is strange to think of osteomyelitis as a local surgical condition, and it is, therefore, rational to look for an agent that will assist in preventing this appalling chain of full-blown septicemia. We have all been familiar with the treatment of the recent past: First and always, surgical interference with the local lesion as soon as it could be identified; later, interference, perhaps when an abscess could be identified, the while the patient had supportive treatment with fluids, *etc.* We have gone through a stage of giving antitoxin. But the mortality records prior to the adminis-

* Read before the American Surgical Association, May 13–14, 1943, Cincinnati, Ohio.

tration of sulphonamides was about 22 per cent in our series. On the whole, the results were poor from the mortality standpoint. There are apparently no records of the mortality rate in cases of osteomyelitis that did not have the benefit of surgery! Yet we have all seen the late case, one that has survived the early acute phase and has come to hospital with a single lesion, either undrained or opened spontaneously. We have seen, too, the case of Brodie's abscess, unrecognized in its formative stage, but discovered and recognized as a lesion of the bone years later. Such cases amply demonstrate nature's ability to deal with the acute phase of osteomyelitis in such a way as to prevent a fatal issue, and, indeed, alone and unaided, to cure the disease. I strongly suspect that so-called undiagnosed and untreated cases would show no such mortality as 20 per cent.

What are the methods used by nature to subdue this invasion? Ninety per cent of the deaths in the past have occurred in the first and second weeks. The natural antitoxin developed as a reaction to toxin is useful in dealing with the toxin elaborated, but has no effect on the extermination of the invader. The human organism, kept from being overwhelmed with poison, is capable of producing and maintaining agencies, phagocytes, bacteriolysin, *etc.*, that directly attack and destroy the invader. While this conflict is progressing, the patient afflicted has all the signs of a reaction, and until the balance is well in favor of the defence, that reaction is very obvious, both generally and locally. From then on there is no real reason why the defence should not greatly increase its power so that the general invasion is wholly under control. The whole system of defence is apparently predicated upon the extermination of the invader, or at least containing him until protective substances can be developed and he can be brought under control. The work of Leveuf[4] gives a good record of a supervised, non-/ or late interfering treatment. It was published before the advent of the sulphonamides, and is a testimony of what is possible by simple medical means and late operation. In his series of 31 cases he had nine deaths, six occurring the day of admission or the following day, one on the seventh day of meningitis, and one on the eighth day of general septicemia. The ninth case was the only one that did not receive early surgical treatment, and he succumbed two months and five days after admission to hospital of cardiac failure. Of the 23 that survived, six had early surgical intervention; three simple incisions of abscess, one trepanning, and two simple resections. The 17 others were treated first medically. Surgical intervention was postponed from three to 49 days, all excepting one being simple incision of abscess. One child had a resection on the ninth day following spontaneous discharge from the epiphysis. One case had no surgical intervention. His rule was to wait for the fall of the temperature before opening the abscess.

It is now well established that the sulphonamide drugs are capable of effecting a condition in the blood that will inhibit the growth of organisms. We should, therefore, test the possibilities of this drug as an aid in treatment.

It would seem rational to attempt to introduce into the blood, at the earliest possible moment, a sufficient quantity of drug to render innocuous, or impotent, organisms that are in the blood stream or in reach of body fluids. In the case of the staphylococcus, particularly, which operates by means of a toxin high in necrotizing qualities and the production of thrombosis, it is urgent to administer the drug at the earliest possible moment and in quantities sufficient to the need. How great the need may be can only be determined accurately after the event, so that the assumption of the need is all that is required for the heavy administration of the drug. It is our practice to give children of about eight years of age 8–10 Gm. daily. We are thus able to maintain levels of from 6 to 12 mg. per cent in the blood. Larger doses may be possible, even desirable, but at this level we have had a number of reactions. The relation between the drug administered and the concentration in the blood varies greatly in different individuals. Some, when given sulphathiazole 10 Gm., will be found to have a blood level of 4 mg. per cent only, while the quantities may be reversed in other cases. For instance, T. H. was given sulphathiazole 6 Gm. daily for 16 days, and her blood level never went higher than 3 mg. per cent. She then had a reaction, and had no drug for two and one-half days. She was then given sulphadiazene 6 Gm. daily, and the blood level rose to 11.9 mg. per cent.

The other cases in this series reacting were as follows:

J. H., age eight and one-half. Given 8 Gm. of sulphathiazole daily for one week, then increased to 10 Gm. daily for five days. Drug discontinued for two days because of high fever. Started on sulphadiazine 10 Gm. daily for nine days, then discontinued because of high fever and rash. All drug discontinued for three weeks, then restarted on sulphadiazine 6 Gm. daily for three weeks, then discontinued because boy was complaining of severe abdominal pain. This stopped when drug was discontinued, and drug has not been restarted. Blood levels 4.5 to 8.5 mg. per cent.

L. L., age nine. Given sulphathiazole 8 Gm. for one week, then discontinued because of rash. All drug discontinued for six days then restarted on sulphadiazine 5 Gm. daily for six days. Rash reappeared so all drug discontinued. Blood levels 4 to 8.3 mg. per cent.

E. F., age nine. Sulphathiazole 8 Gm. daily for nine days, then sulphadiazine 9 Gm. daily for seven days, then all drugs discontinued because of high fever and rash. Blood levels 2 to 13.9 mg. per cent.

R. N., age ten. Sulphathiazole 8 Gm. daily for 13 days, then discontinued because of high fever. No drug for 24 hours, then started on sulphadiazine 8 Gm. daily. Was able to tolerate sulphadiazine for several months in different dosages. Blood levels 6.5 to 12.3 mg. per cent.

J. LaR., age ten. Sulphathiazole 7 Gm. daily for 13 days, then discontinued because of high fever. Restarted on sulphadiazine, which he tolerated for a long period of time in different dosages. Blood levels 3.3 to 12 mg. per cent.

B. W., age eight. Sulphathiazole 6 Gm. for four days, then discontinued

for 24 hours, then restarted on sulphadiazine 8 Gm. daily. Blood levels 1 to 10.1 mg. per cent.

It has been proved that pathogenic organisms can become drug-resistant, and that probably also happens with staphylococcus and streptococcus.[5] This would lead us to believe in large doses while the organism is still vulnerable. Reactions to the drug in use may make it necessary to discontinue its administration. Thus, when a patient is having sulphathiazole administered shows signs of a rash, high temperature, nausea, or blood in the urine, we discontinue it for a few days and then begin again with sulphadiazine. It has been found that this may then be borne for the remainder of the period desired.

The question of initial large doses is so urgent that one is not justified in testing out the patient to estimate his ability to tolerate the drug. There is apparently no evidence available that patients who do not tolerate the drug without reaction are not benefited from its action. The sensitivity or allergy occurring in some patients from the drug cannot be foretold in all cases by skin tests, as some giving no skin reaction may react violently to the drug.[6]

There is not as much nausea caused by the drug as is commonly believed. It should be remembered that the very ill patient is often nauseated before the administration of the drug, and nausea is not a valid reason for not giving the drug. The problem of the period during which the drug should be administered is primarily involved with the need, and, secondarily, with the sensitivity that develops in the patient.

The drug does not militate against the patient's ability to develop his protective substances against the toxin of the bacteria. While antitoxin has been found to have been ineffective in having any bactericidal value *per se*, yet it is known to neutralize the toxin. Sulphonamides do not inhibit the antigenic power of the toxin. While there is much less toxin produced from degenerating organisms, still what toxin there is has the power to raise the natural antitoxin against the specific infection—witness the rise in the staphylococcus titers in the cases in his series. This is an important point, as the production of immune bodies is of great value in overcoming an infection. Again, the rise in the staphylococcus titer of a patient is of diagnostic value as to the recognition of the organism, since in cases that have received treatment early it is not often possible to recover the germ from either the blood or the local lesion where the latter is not opened.

The question of positive blood culture is one that is frequently discussed as being an evidence of the degree of infection present. A study of our cases does not appear to follow any such pattern. The constancy of the finding of organisms in the blood of a patient cannot be accurately foretold from his clinical condition. Experimentally, we know that a lethal dose of organisms may be introduced into the blood and in a few minutes none can be recovered, and later can be recovered.[7] Since the introduction of sulphonamides the picture of the relationship of positive or negative cultures to degree of infection is more obscure than ever. The only rational basis for study of the disease

seems to me to consist in the presence of a local lesion, roentgenologic changes being obligatory. In addition, there may be the recovery of the germ from the blood or pus, and the staphylococcus titer which indicates the specific reaction to the antigen of the toxin. When these conditions are fulfilled one has osteomyelitis.

Reports of cases treated by use of the drug, with no incision of the lesion in bone, have been reported by Hoyt, *et al.*[8] They report no deaths in the 12 cases reported. These cases were all staphylococcus. This series constitutes a unique record, and must give thoughtful surgeons reason to reassess the whole problem of the treatment of acute osteomyelitis. If cases will survive spontaneously, on the one hand, and if 12 consecutive cases will survive the acute phase with medication by sulfonamides, the part played by surgical incision of the local lesion is certainly not a factor in saving life.

TABLE II

OSTEOMYELITIS (JANUARY, 1940—MAY, 1943)

All Received Sulphonamides

Total number of cases	89
Number of cases with late incisions of abscess	64
Number with no operation	25
Number died:	
Moribund on admission	3
One case incised	1
Mortality rate	4.2%

TABLE III

DEATHS

All 4 deaths were *hem. staph. aureus* cases.
D. B. died 13 hrs. after admission, undiagnosed.
D. W. died 25 hrs. after admission.
J. A. died 1½ hrs. after admission.
T. C. died 3½ weeks after admission.

Our records of 89 cases, three moribund on admission, show, since sulphonamide administration, 25 not operated upon, and none dead, the others operated upon, and one dead; in all a mortality rate of 1.2 per cent, excluding the case moribund on admission. These results are not such that, from the mortality standpoint, incision can be altogether condemned when added to sulphonamide medication (Tables II and III).

An analysis of the case that died on the 31st day, after being in hospital 24 days, is illuminating. He was ill; had positive culture, and a sharp reaction. He developed an obvious superficial abscess over the upper part of the tibia. The knee contained thin pus, from which staphylococcus was recovered. On the 17th day, when his temperature was about 100°–100.5° F., his pulse rate 95, taking without reaction sulphathiazole 9 Gm. daily, with a blood level of 8 mg.%, it was decided to drain the abscess and the knee. This was done. The knee joint was opened and a soft rubber drain pushed

through the suprapatellar pouch from side-to-side. The abscess in the leg was drained. His condition the next day was much worse, temperature up, and pulse up to 120–130. He developed no new bone lesions, but he died 14 days later (Table IV). It now seems to me that the surgical interference in this case turned the scales in favor of the infection. The drainage of the knee and the abscess in the leg did not prevent the death of the boy from the spread of the disease to all the regions of his body. The result could not have been worse with no treatment of any kind. I now believe that had he had no operation he would probably have survived his acute infection. Cases that have appeared equally ill, with just such abscess and local and general symptoms, have survived when they have not been subjected to incision.

TABLE IV

Patient, Thomas Cosgrove

Admitted June 12, 1942 — Died July 6, 1942
Positive blood culture — Drainage June 22, 1942
Sulphathiazole 7.5 Gm. daily for 24 days
Blood level over 6 mg. %
Titer—June 12—2 su/cc., June 24—17 su/cc., July 3—7 su/cc.

Anatomic Diagnosis

1. Acute osteomylitis of lt. tibia (*hem. staph. aureus*)
2. *Hem. staph. aureus* septicemia
3. Abscesses of lungs, kidneys, and left chest wall
4. Acute suppurative myocarditis
5. Acute cardiac dilatation
6. Early acute pericarditis
7. Pleural effusion (bilateral)
8. Fatty liver and acute congestion of liver
9. Edema of gallbladder
10. Fibrous pleural adhesions (right)
11. Petechial hemorrhages—epicardium, endocardium, urinary bladder mucosa
12. Patent foramen ovale

In the subsidence in the acute phase a dramatic change takes place. It occurs over a period of 10–12 hours. The general reaction of the patient subsides; the intense swelling of the soft tissue at the local lesion diminishes; the underlying abscess becomes more obvious in its outline; and the patient is comparatively comfortable. Later, the abscess may increase or diminish in size. When it subsides it may, in the course of three or four weeks, entirely disappear. In conditions where it becomes more superficial and enlarged it may so involve the skin that it spontaneously opens through a small opening. In our small experience, in a case where a sinus of this type is formed, there has been no large sequestrum present in the underlying bone. There are, however, small areas in the bone lined with granulation tissue and containing very small, fragile sequestra. Mostly, the cavities are subperiosteal and contain granulation tissue only. It seems that unless the abscess is too superficial it will not drain of itself and will tend to subside, and behave in every particular like a tuberculous abscess. Any dead bone within it may be disposed of by the action of the tissues and their fluids or may become regenerated. It may be said that a sequestrum may be dealt with spontaneously unless a sinus develops or be made, in which circum-

stance it will be necessary to remove it before the sinus will heal. The pathologic change in bone, as evidenced roentgenologically, is different to that of cases where lesions are drained. In drained lesions there is generally a wide destruction of bone together with a large involucrum; sequestration is present in over half of the cases. The first change that can be

TABLE V

CASES NOT OPERATED UPON

Hosp. No.	Name	Age	Day of Disease	Bone	Bact.	Staph. Titer	Drug	Blood Level	Result
72,096	E.C.	11	7	Calcaneus	Neg.	4–12.5	Sth.* 8 Gm.	3.9–5.9	Closed
117,812	F.S.	8	14	Femur	Neg.	12	Sth. 7 Gm.	3.5–4.2	Opened spon. Sm. sequestrum
118,696	A.A.	9	21	Tibia	S.A.	13	Sth. 8 Gm.	4.3–10.2	Closed
123,232	J.L.	10	2	Tibia	S.A.	1.6–25	Sth. 4 Gm. Sd.† 8 Gm.	3.2–12	Closed
123,929	R.N.	10	4	Femur	S.A1.	3–5	Sth. 8 Gm.	9.9–2.3	Closed
124,120	W.H.	6	21	Tibia	S.A.	4–28	Sth. 8 Gm. Sd. 8 Gm.	6.2–11.4	Closed
124,241	D.S.	8	14	Humerus	Neg.	12.5	Sth. 8 Gm. Sd. 8 Gm.	5.5–12.5	Opened spon. Sm. sequestrum
124,830	G.A.	13	8	Femur	Neg.	1–3.5	Sth. 8 Gm.	4–13.9	Closed
119,809	T.N.	5	11	Femur	Neg.	4–4.2	Sth. 8 Gm.	3.7–7.7	Closed
120,043	F.D.	7	4	Femur	Neg.	0.5–9.8	Sth. 4 Gm.	4.3–5.7	Closed
123,549	J.M.	10	6	Femur	S.A.	1.5–3	Sth. 4 Gm. Sd. 8 Gm.	4.5–11.8	Closed
124,464	J.W.	12	5	Cuboid	S.A.	2.5–12	Sth. 8 Gm.	8–10.2	Closed
125,463	J.B.	13	3	Femur	Neg.		Sth. 8 Gm.	8.2–13.2	Closed
125,230	J.F.	11	6	Femur Tibia	Neg.	3–6.6	Sth. 8 Gm.	4–8.8	Closed
122,526	B.H.	2	7	Tibia	Neg.	1.5–3.5	Sth. 8 Gm.	8.2	Closed
125,451	E.F.	8	10	Tibia	S.A.	10	Sth. 8 Gm. Sd. 8 Gm.	2–13.8	Opened spon. Sm. sequestrum
126,302	L.L.	9	3	Tibia	S.A.	2–2.6	Sth. 8 Gm. Sd. 6 Gm.	4.8–12	Closed
126,317	J.H.	8	7	Tibia	S.A.	2–25	Sth. 9 Gm.	4–8.4	Opened spon.
114,044	H.H.	3	2	Femur	Neg.	1.4–4.6	Sth. 5 Gm. Sd. 6 Gm.	4–12.2	Closed
126,819	F.N.	8	4	Tibia	Neg.	2–3	Sth. 8 Gm.	6–14.8	Closed
126,945	T.H.	14 mo.	7	Femur	S.A.	7–5.4	Sth. 6 Gm. Sd. 6 Gm.	2–11.5	Closed
126,895	K.N.	4	14	Femur	S.A.	8–5.8	Sth. 5 Gm.	4.2–6.4	Still in hospital
127,380	B.W.	8	5	Tibia	S.A.	1	Sth. 8 Gm.	1–8.4	Still in hospital
127,402	H.M.	9	5	Femur	S.A.	0.6	Sth. 7 Gm.	1.2–6.4	Still in hospital
115,763	M.W.	3	24	Lumbar vert.	Neg.	5.5–6.5	Sth. 1.5 Gm.	2.1–16.2	Closed

* Sth. = sulphathiazole. † Sd. = sulphadiazine.

recognized in bone of undrained cases occurs about eight or ten days. From then on the lesion continues to lose density, and involucrum very much diminished in extent, sometimes hardly present, may be seen. There is no obvious death of a large mass of bone, except in rare cases, and sequestration is present in about 10–15 per cent of cases only. Secondary lesions in other bones are rare, and when they do occur, their course is very much attenuated, and a nonvirulent process with mild pathologic changes (Table V).

1A 1B

FIG. 1A.—T. N. Six and a half weeks after onset of illness. Drug estimation in blood 4.6 mg. %. Titer 4.2 su/cc.

FIG. 1B.—T. N. Fourteen months after onset of illness. Epiphysis affected. Pus with staphylococci aspirated from joint. Diagnostic aspiration from joint.

2A 2B 3A 3B

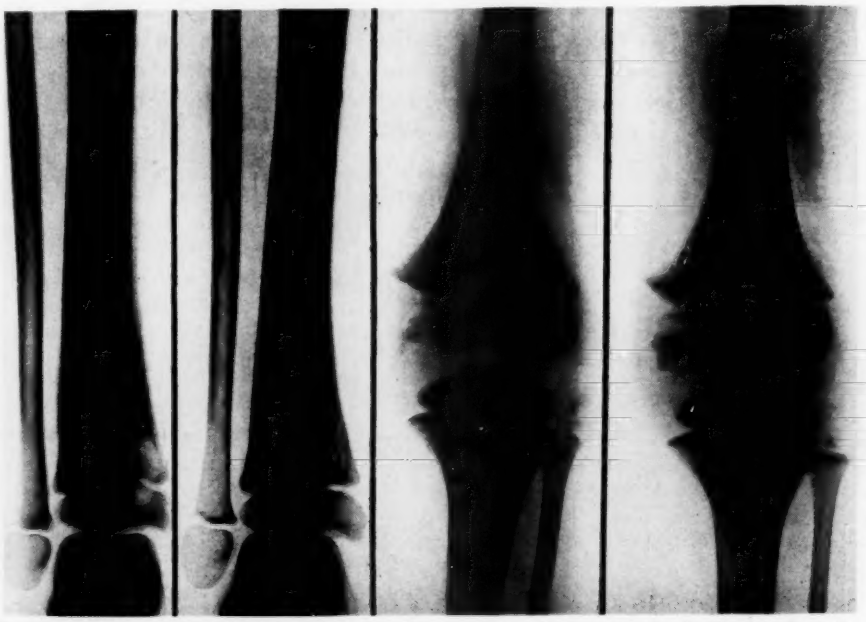


FIG. 2A.—W. H. Twenty-sixth day of illness. Titer 7.5 su/cc. Drug estimation in blood 10.8 mg.%.

FIG. 2B.—W. H. Six months after onset of illness.

FIG. 3A.—K. N. Two months after onset of illness. Titer 9.5 su/cc. Drug estimation in blood 14.6 mg.%.

FIG. 3B.—K. N. Four months after onset of illness. Titer 16.6 su/cc. Drug estimation in blood 8.3 mg.%.

We have had cases where contiguous joints have been involved, in one instance the organism was recovered from a knee joint, where the epiphysis of the femur was involved. This case did well, and soon became afebrile, with the knee returning to normal size, and with a fair cartilage space and movement. The swelling of joints near the lesion quickly subsides and the joints recover their normal freedom of movement very quickly.

From the complete subsidence of the abscess in some cases, and from its apparent nontoxic presence in others, there seems to be no urgent reason for interfering with it.

The cases treated in this series have had ordinary supportive treatment, together with sulfonamides. We have used sulfathiazole, but it would appear that sulfadiazine is more readily borne and can be taken over a longer period of time, and a higher blood level can be maintained. It may be a better drug for the treatment of osteomyelitis. We have used no splinting except where a joint was involved, then traction was sometimes employed.

The diagnosis of the condition is to be made from first—the history: The history of a skin lesion is nearly always available when the questioning is intelligent; second, the examination of the general reaction; and third, the examination of the part. No accurate localization of the lesion, as to whether it be in the epiphysis, the metaphysis or the periosteum, is necessary. This information will be available from the roentgenograms in eight to ten days. There may be also present about that time a local abscess that can be examined without pain or discomfort to the patient. The drug should be given early in the disease and in adequate amounts. When it is, the disease will not be able to make much headway, and the mortality will be found only in those cases that are moribund of the infection before the true nature of the disease has been recognized and, thus, have not had the advantage of adequate doses of sulfonamides.

CONCLUSIONS

There is reason to believe that the administration of sulfonamides in heavy doses early in the disease may prevent deaths occurring from this disease.

An early recognition of the true character of the disease from the history, and the general and local symptoms is essential to adequate medication.

The medication must be adequate, that is, large doses must be given early.

Incisional interference is not a factor in saving lives, and may be a very deleterious proceeding.

REFERENCES

[1] Stookey, P. F., *et al.*: S. G. O., **63**, August, 1936.

[2] Lexer, Erich: General Surgery, New York and London, D. Appleton & Co. (Bibliography) 236–262, 1908.

[3] Hobo, Teruro: Zur Pathogenese der akuten haematogenen Osteomyelitis. Acta Scholae Med. Univ. Kiota, **4**, 1, Bibliography, 1921.

4 Leveuf, J.: Academie de Chirurgie, **298,** 1936.
5 Lancet, **369,** March 20, 1943.
6 Lancet, **339,** March 13, 1943.
7 Martin, Walton: ANNALS OF SURGERY, **82,** 1925.
8 Hoyt, *et al.*: J. A. M. A., **117,** 2043, 1941.

DISCUSSION.—DR. KELLOGG SPEED (Chicago): Doctor Robertson's title must be taken literally to assay his results and to confine our attention to acute hematogenous osteomyelitis—namely, an infection disseminated *via* the blood stream (of staphylococcus in over 80 per cent) usually from skin or soft parts, less often from the mucous surfaces of nasal passages and throat or tonsils, and carried to the bones of adolescents. There may be some failures from medical treatment on account of the type of bacteria. Also, chemotherapy, even if pushed by intravenous methods to a level of 12 or 15 mg. per cent, may fail in some instances to maintain sufficient bacteriostatic power to overcome the rapidity of production and pouring out of the bacteria into the blood. The earlier the drug is administered, the more powerful its control over the spread to the host's tissues and bone—ideally before any bone lesion is known to all. The percentage of occurrence of acute infectious osteomyelitis is falling off in some districts because the sulfonamides are widely employed in treatment of nasal and skin infections, acting bacteriostatically before osseous lesions may develop. After early medical treatment by massive doses we can believe that the results in a consecutive series of patients would be even better than the use of the drug plus early local and extensive operation which would interfere with the local blood supply of the bone, lower the resistance locally, and block the bacteriostatic action of the drug. My experience with this form of osteomyelitis in the bodies of the vertebrae, treated without operation, has been sad—three patients succumbing after long periods, in spite of massive dosage of the sulfa compound. However, I am limiting operation to drainage of known bone abscess and using repeated joint aspiration before open drainage.

Among the recent reports, I believe that made by Gage is most noteworthy. Any concept of the osteomyelitis must take into consideration the action of the toxins developed; especially the purely necrogenic, and that part of the toxin which increases the spread of bacteria. If the sulfonamides can paralyze bacterial growth, and thus limit or prevent the freeing of toxins, the whole chain of events, including thrombophlebitis, the number of colonies free in the blood, and ultimately the amount of bone destruction resulting, will be reduced or aborted. A late bone or subperitosteal abscess may be absorbed by leukocytes and recticulo-endothelial tissues after the action of bacteriolysins and agglutinins. Sequestra may rarely form, and an involucrum need not appear in its absence. Wilson and McKeever, in their series of 32 cases in Los Angeles, found palpatory evidence of involucrum in some, but at operation later saw only hyperplastic bone and no abscess. Together with Wilenski, they still favor operation for established osteomyelitis. Gage insists on daily administration of 60,000 to 100,000 units of potent antistaphylococcic serum until toxemia subsides. In the mild infections practically no bone change may appear as the toxins failed to kill bone; others may terminate as Brodie's abscess, with only a small local death of bone. The results also vary on the point of localization within the bone of the carried in infection. If it starts to an easy spread *via* the marrow, comparable to a rapid lymphatic spread, we can look for a wider death of bone and more pus; if it starts in or near the cortex and spreads only locally under periosteum, the result may be localized abscesses pointing to the surface, relatively easy to drain.

Additional reports will probably verify Dr. Robertson's results. We await also, reports on the use of penicillin, which is nontoxic and especially adapted to bacteriostatic action against the staphylococcus and all gram-positive forms of bacteria. While it has not yet proven of value in subacute bacterial endocarditis, in dosages of 30,000 to 40,000 Oxford units in 24 hours, according to Herrell, it does clear the blood stream of bacteria and may act favorably in acute infectious osteomyelitis.

DR. ALBERT KEY (St. Louis, Mo.): I agree with Dr. Robertson that the time to treat osteomyelitis with sulfonamides is before it starts, and after it starts I think one should realize that the efficiency of the sulfonamide varies inversely with the number of organisms present in a given focus, and inversely with the amount of necrotic tissue present in a given focus. It is for that reason that sulfonamides will clear the blood stream and not sterilize the focus in the bone.

I have seen a few cases of osteomyelitis that have had what the doctors who were treating them thought was the limit of sulfonamide therapy, in which the disease has progressed to the point where they got pathologic fractures. They got involvement of joints and they got widespread destruction of bone.

The question in my mind, and one which I am not yet able to decide, is: Does an incision for drainage—and by that I do not mean an extensive operation but an incision for drainage—lower the resistance locally to infection in the bone or anywhere else? Until there is some evidence to prove that, I believe that when, and if, you can diagnose the presence of an abscess in bone and your patient is in good condition, that should be drained. You should also give them sulfathiazole, all you think they can take.

The other question is: How long are you going to keep up your sulfathiazole? In my experience, these cases treated with sulfathiazole, and sulfathiazole alone, have formed sequestra after the sulfathiazole was stopped. After function of the limb was resumed they have flared-up again and have eventually required operation for drainage and removal of sequestra.

I still feel that there is a very definite place for surgery in the treatment of acute osteomyelitis, and that that place is the drainage of the abscess as soon as the patient is in condition to stand the operation. I do not believe that the drainage in the case that Doctor Robertson showed was responsible for that boy's death. He died of septicemia, and he died about 14 days after his operation.

DR. D. E. ROBERTSON (Toronto, Ontario, closing): I do not think I have anything to add, except to say what I might have said before, that those children who do not tolerate sulfathiazole were given sulfadiazine. I think probably it is just as good a drug, and I think with sulfadiazine one can maintain a higher level than with sulfathiazole, and it is much better borne.

I want to say, in conclusion, when the child is recovering, and is well of the acute phase, and can stand an operation for the drainage of abscess, just consider whether or not it is necessary to drain the abscess. The child has gotten well with an abscess. The secondary soft tissue swelling around the abscess has subsided, leaving the abscess so you can examine it and delineate it easily. It is slightly tender.

I think we make a great mitsake draining these abscesses just because they are easily accessible. I think when we do attack them, we probably do something that is not in the best interests of the patient. At all events, when they are left without incision the results are excellent, much better in my opinion than those incised.

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY

Walter Estell Lee, M.D.
1833 Pine Street, Philadelphia, Pa.

Contributions in a foreign language when accepted will be translated and published in English.

Exchanges and Books for Review should be sent to James T. Pilcher, M.D., Managing Editor, 121 Gates Avenue, Brooklyn, N. Y.

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY
East Washington Square, Philadelphia, Pa.